Urological Oncology

The Prognostic Factors for Patients with pT1a Renal Cell Carcinoma

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Purpose: Although the prognosis of patients with pT1a stage renal cell carcinoma (RCC) is generally good, some of these patients show distant metastasis. In this study, we intended to identify the perioperative and pathologic prognostic factors for patients with pT1a stage RCC.

Materials and Methods: A total of 93 patients who were diagnosed with pT1aN0M0 RCC between January 1995 and December 2004 were included. All the patients underwent radical (n=63, 67.7%) or partial (n=30, 32.3%) nephrectomy by a single surgeon. Preoperative data [age, sex, body mass index (BMI), and the presence of symptoms], follow-up duration, surgical methods, and pathological parameters (tumor size, tumor location, histologic type, Fuhrman's nuclear grade and the presence of microvascular invasion, hemorrhage, necrosis, calcification, and a cystic component in the tumor) were retrospectively analyzed to identify which of these were prognostic factors for pT1a RCC.

Results: The patients' mean age was 55.0±11.4 years and the mean follow-up duration was 63.6±31.1 months. The 5-year cancer-specific survival rate and the 5-year recurrence-free survival rate were 100% and 88.1%, respectively. Nine patients (9.7%) showed distant metastasis, but local recurrence was not shown. Fuhrman's nuclear grade (p=0.040, OR=5.147), microvascular invasion (p=0.011, OR=13.500), and tumor necrosis (p < 0.001, OR=26.000) had a significant impact on distant metastasis in the univariate analysis. The multivariate analysis subsequently showed that microvascular invasion (p=0.033, OR=17.947) and tumor necrosis (p=0.002, OR=15.922) were independent prognostic factors.

Conclusions: Microvascular invasion and tumor necrosis are the prognostic factors for patients with pT1a RCC.

Key Words: Prognosis; Renal cell carcinoma

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INTRODUCTION

The proportion of renal cell carcinoma (RCC) that is diagnosed as pT1a is known to have recently increased [1]. Advances in diagnostic imaging, such as ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging, have led to an increased incidence of finding small-sized renal tumors [1,2]. Although patients with pT1a RCC generally have a good prognosis, some patients who have undergone nephron-sparing surgery or radical nephrectomy show a local relapse at the previous surgical site or distant metastasis [3]. Several clinical, anatomical, histological, and immunohistochemical features have been suggested to be prognostic factors for disease progression and survival [4], but most of the proposed prognostic factors are based mainly on the data for large-sized RCCs. Unfortunately, the ability to predict the biological potential of small RCCs remains limited, and so patient counseling and clinical decision making remain suboptimal. Dall'Oglio et al reported that RCC is a singular disease with a highly variable natural history and that identifying a reliable set of prognostic factors may improve the treatment of patients with this disease [4]. Therefore, it is important to define the prognostic factors of small RCC. In this study, we intended to identify the perioperative and pathologic prognostic factors for patients with pT1a stage RCC.

MATERIALS AND METHODS

1. Patients

A total of 93 patients who were diagnosed with pT1aN0M0 RCC between January 1995 and December 2004 were included in this study. All of the patients underwent radical or partial nephrectomy by an experienced surgeon. Among the patients, 63 patients (67.7%) underwent radical nephrectomy and 30 patients (32.3%) underwent partial nephrectomy.

2. Preoperative and postoperative evaluations

The preoperative evaluations consisted of assessing the age, sex, and body mass index (BMI) of the patient and the presence of symptoms. The postoperative evaluations consisted of assessing the surgical methods and pathologic parameters (tumor size, tumor location, histologic type, Fuhrman's nuclear grade and the presence of capsule invasion, microvascular invasion, hemorrhage, necrosis, calcification, and a cystic component in the tumor). The pathologic parameters were evaluated by an experienced pathologist.

3. Follow-up evaluations

All the patients received a follow-up visit at 1 to 2 weeks after discharge for assessing their general health status. After the first visit, the patients received follow-up evaluations at every 3 or 6 months for the first year and then annually. At these times, they were evaluated for newly developed symptoms and they underwent careful physical examinations, laboratory tests, and radiologic tests (chest X-ray, USG, CT). The USG or CT was evaluated for local recurrence or distant metastasis.

4. Definition

The stage was reassessed according to the 2002 TNM classification system [5]. The RCC histologic type was classified according to the current WHO classification system [6].

TABLE 1. The characteristics of 93 patients with pT1a renal cell carcinoma

Characteristics	No. of patients (%)
Mean age (years)±SD	55.0±11.4
Sex	
Male	64 (68.8)
Female	29 (31.2)
Mean BMI (kg/m^2)±SD	23.3±3.1
Preoperative symptoms	
Flank pain	7 (7.5)
Abdominal discomfort	2 (2.2)
Weight loss	1 (1.1)
Follow-up duration (months)	63.6±31.1 (10-159)
Surgical methods	
Radical nephrectomy	63 (67.7)
Partial nephrectomy	30 (32.3)
Tumor size (cm)	2.9±0.8 (1.1-4.0)
Tumor location	
Upper pole	38 (40.9)
Mid pole	34 (36.5)
Lower pole	21 (22.6)
Histologic type	
Clear cell	79 (85.0)
Papillary	11 (11.8)
Chromophobe	3 (3.2)
Fuhrman's nuclear grade	
Grade 1 or 2	52 (55.9)
Grade 3 or 4	41 (44.1)
Capsule invasion	8 (8.6)
Microvascular invasion	6 (6.5)
Hemorrhage in tumor	42 (45.2)
Necrosis in tumor	12 (13.0)
Calcification in tumor	4 (4.3)
Cystic component in tumor	23 (24.7)

BMI: body mass index
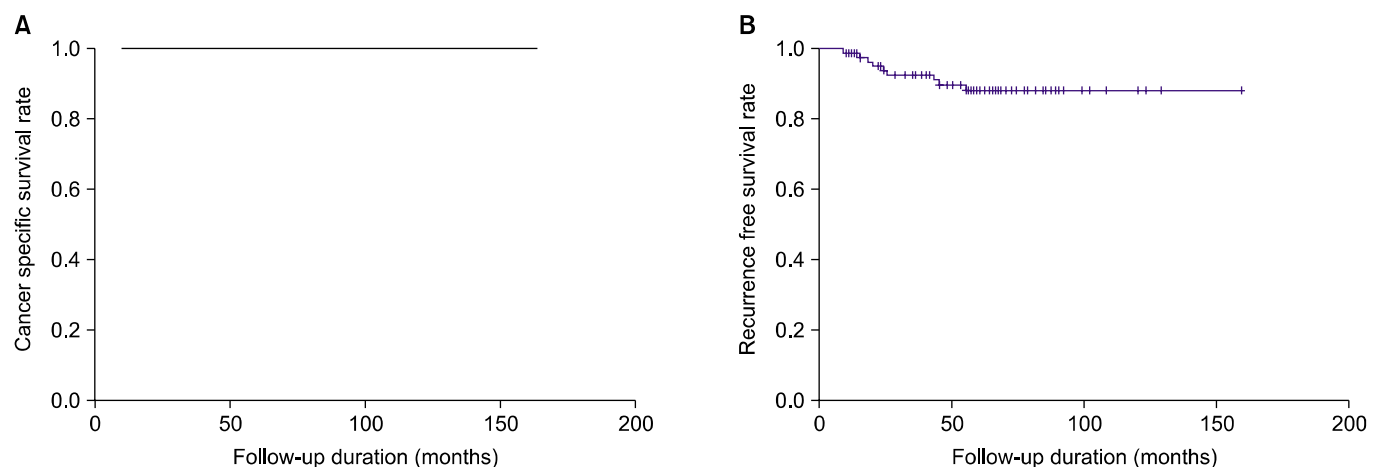
FIG. 1. The 5-year cancer-specific survival (A) and the 5-year recurrence-free survival (B) for all the patients with pT1a renal cell carcinoma. The statistical analysis: (A) Life-table method, (B) Kaplan-Meier survival analysis.

5. Analysis

The preoperative and postoperative factors were statistically analyzed together with the presence of local recurrence or distant metastasis to identify the prognostic factors for patients with pT1a RCC. Univariate analysis was performed by using Fisher's exact test and the chi-square test. Multivariate logistic regression analysis was used to determine the independent prognostic factors affecting local recurrence or distant metastasis. Kaplan- Meier survival analysis and the life-table method were used to determine the 5-year cancer-specific survival rate and the 5-year recurrence-free survival rate. A 5% level of significance was used for all statistical testing, and all statistical tests were two-sided. The analysis was performed by using the statistical software SPSS (17.0KO for Windows, Release 14.0.2; SPSS Inc, Chicago, IL, USA).

RESULTS

The patients' mean age was 55.0 ± 11.4 years, and of the 93 patients, 64 (68.8%) were men and 29 (31.2%) were women. The characteristics of the 93 patients with pT1a RCC are shown in Table 1. The 5-year cancer-specific survival rate and the 5-year recurrence-free survival rate were 100% and 88.1%, respectively (Fig. 1).

Nine patients (9.7%) showed distant metastasis and none showed local recurrence at a previous surgical site. Among the 9 cases with distant metastasis, the lung (4.3%) was the predominant metastatic site. Distant metastasis also occurred in the liver (2.1%), bone (1.1%), brain (1.1%), and contralateral kidney (1.1%) (Table 2).

Among all the investigated prognostic factors, Fuhrman's nuclear grade (p=0.040, OR=5.147), microvascular invasion (p=0.011, OR=13.500), and tumor necrosis (p< 0.001, OR=26.000) had a significant impact on distant metastasis in the univariate analysis. Other factors such as age, sex, BMI, preoperative symptoms, surgical methods, tumor size, tumor location, histologic type, and the presence of capsule invasion, hemorrhage, calcification, and a cystic component in the tumor were statistically insignificant. Among the 9 patients with distant metastasis, 3 patients (33.3%) showed microvascular invasion and 6 patients (66.7%) showed tumor necrosis. The presence of microvascular invasion and tumor necrosis showed distant

metastasis in 50% of the cases, respectively (Table 3).

Multivariate analysis subsequently showed that microvascular invasion (p=0.033, OR=17.947) and tumor ne-

TABLE 2. Local recurrence and distant metastasis in the patients with pT1a renal cell carcinoma

	No. of patients (%) (n=93)
Local recurrence	0 (0)
Distant metastasis	9 (9.7)
Lung	4 (4.3)
Liver	2 (2.1)
Bone	1 (1.1)
Brain	1 (1.1)
Kidney (contralateral site)	1 (1.1)

TABLE 3. Univariate analysis of the prognostic factors for distant metastasis in the patients with pT1a renal cell carcinoma

	Meta-stasis (n)	No meta-stasis (n)	p-value[a]	Odds ratio
Age (years)				
≤60	3	57	0.064	4.222
>60	6	27		
Sex				
Male	5	59	0.453	1.888
Female	4	25		
BMI (kg/m^2)				
<23	5	48	1.000	1.067
≥23	4	36		
Preoperative symptoms				
Absence	8	75	1.000	1.042
Presence	1	9		
Surgical methods				
Radical nephrectomy	9	54	0.054	0.643
Partial nephrectomy	0	30		
Tumor size (cm)				
<3	2	40	0.177	3.182
≥3	7	44		
Tumor location				
Upper pole	3	35	0.743	-
Mid pole	3	31		
Lower pole	3	18		
Histologic type				
Clear cell	8	71	0.222	-
Papillary	0	11		
Chromophobe	1	2		
Fuhrman's nuclear grade				
Grade 1 or 2	2	50	0.040	5.147
Grade 3 or 4	7	34		
Capsule invasion				
Absence	7	78	0.172	3.714
Presence	2	6		
Microvascular invasion				
Absence	6	81	0.011	13.500
Presence	3	3		
Hemorrhage in tumor				
Absence	6	45	0.506	0.577
Presence	3	39		
Necrosis in tumor				
Absence	3	78	<0.001	26.000
Presence	6	6		
Calcification in tumor				
Absence	9	80	1.000	0.952
Presence	0	4		
Cystic component in tumor				
Absence	9	61	0.106	0.726
Presence	0	23		

BMI: body mass index, [a]: Fisher's exact test

crosis (p=0.002, OR=15.922) were independent factors that had an impact on distant metastasis (Table 4). The survival rate of the patients with microvascular invasion was significantly lower than that of the patients without microvascular invasion (p < 0.001). The survival rate of the patients with tumor necrosis was also significantly lower than that of the patients without tumor necrosis (p < 0.001) (Fig. 2).

DISCUSSION

The incidence of RCC has increased in the past decades, with the greatest increase being patients with small renal tumors. This has led to a migration of RCC cases toward earlier stages, and the incidence of RCC continues to grow about 3% annually [7]. The widespread use and development of radiologic imaging techniques has increased the detection of incidental small RCCs.

Various prognostic factors for RCC such as symptoms, tumor size, histologic type, Fuhrman's nuclear grade, tumor stage, the presence of lymph node metastasis, and the presence of tumor necrosis have been evaluated in numerous reports [8,9]. The prognostic value of histopathological factors such as tumor stage and grade has been most frequently reevaluated, and these are considered to be the most important prognostic factors [8]. But for many cases,

tumor stage and grade only are not sufficient to predict the clinical features [10,11]. Therefore, it is of clinical significance to find other prognostic factors that can predict the clinical features of RCC. In this study, Fuhrman's nuclear grade, microvascular invasion, and tumor necrosis were the significant factors that predicted distant metastasis. Of these, microvascular invasion and tumor necrosis were the independent prognostic factors.

The molecular behavior and progression of RCC, as well as the evaluation of the clinical and pathological predictive factors, have recently led to the suggestion of new algorithms to define the prognosis of patients with RCC [12]. In addition to the well established prognostic factors such as the TNM stage, tumor size, and Fuhrman's nuclear grade [8], the presence of microvascular tumor invasion and tumor necrosis in RCC are considered to be important predictors of disease progression and recurrence [13-20]. Nevertheless, pathological reports of microvascular invasion and tumor necrosis in renal cancer are still not common in the Korean or international medical literature.

Angiogenesis has an essential role in pathological conditions such as RCC, and angiogenic factors are critical for the initiation and maintenance of the vascular network. Malignant cells perpetually stimulate the host's stromal and vascular cells towards physiological invasion. In the same microenvironment, vascular sprouts migrate and invade toward the tumor while the tumor cells migrate outward in the opposite direction. It is known that vascular endothelial growth factor (VEGF) stimulates vascular permeability along with intravascular growth and neoplastic cell invasion. It is well known that RCC is characterized by abundant neovascularization, and metastases have been more frequently found in patients with highly vascularized primary RCC [21]. Microvascular invasion is explained by the existence of tumor cells in the walls of the microvessels, along with endothelial cells that are locally damaged due to the tumor cells [13,16].

Dall'Oglio et al showed that microvascular invasion is an

TABLE 4. Local recurrence and distant metastasis in the patients with pT1a renal cell carcinoma

	Odds ratio	95% confidence interval		p-value[a]
		Lower	Upper	
Fuhrman's nuclear grade	9.942	0.815	121.308	0.072
Microvascular invasion	17.947	1.261	255.376	0.033
Necrosis in tumor	15.922	2.735	92.699	0.002

[a]: logistic regression analysis
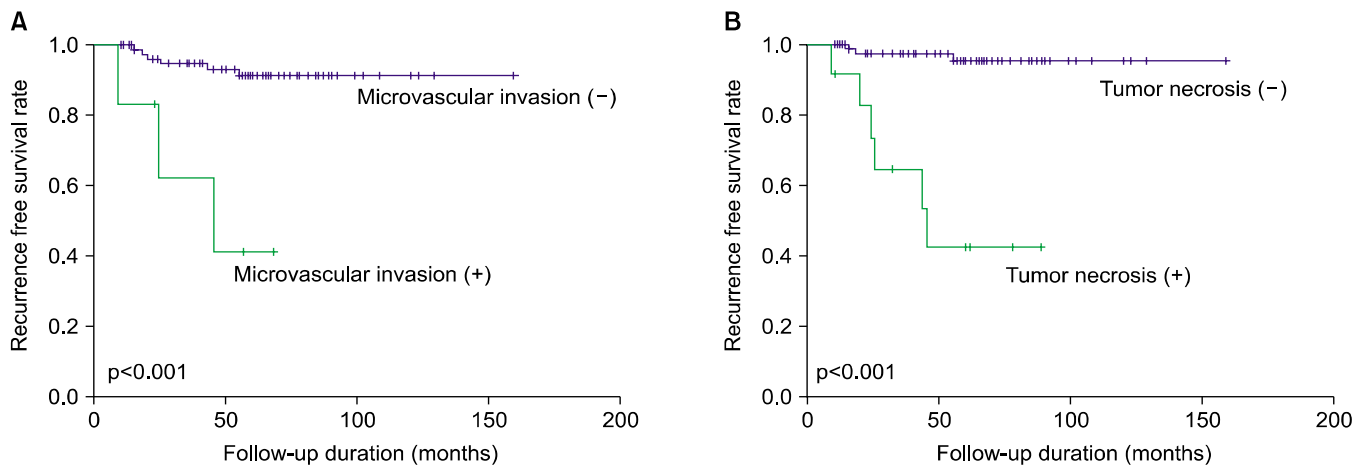
FIG. 2. Kaplan-Meier survival curve estimates of the 5-year recurrence-free survival for all patients according to (A) microvascular invasion and (B) tumor necrosis.

important independent risk factor for disease-free survival (87% vs. 27%) and cancer-specific survival (88% vs. 40%) for patients with surgically treated RCC who are negative or positive for microvascular invasion, respectively [12]. Van Poppel et al reported a 39% rate of disease progression for tumors with microvascular invasion, whereas only 6% of patients with no microvascular invasion had progression [15]. Mrstik et al reported 5-year survival rates of 35% for patients with microvascular invasion and 90% for the remaining patients [14]. In another study, Dekel et al reported similar findings, with disease progression rates of 55.5% for patients with microvascular invasion [17].

Tumor necrosis was initially recognized in the 1970s as a predictor of aggressive RCC behavior [22]. Various studies have tried to evaluate the prognostic relevance of tumor necrosis as related to disease-free survival and cancer-specific survival, and some investigations have reported a significant influence of tumor necrosis on the survival of RCC patients. Han et al reported a 5-year survival rate of 72.2% for stage pT1a patients with tumor necrosis and 93.6% for stage pT1a patients without tumor necrosis [19]. In another study, RCC patients without tumor necrosis showed a 2 to 3 times higher survival rate than that of the patients with tumor necrosis [23,24].

In this study, the presence of microvascular invasion and tumor necrosis in the pT1a RCC patients showed a 50% rate of distant metastasis, respectively. This showed that these factors should not be overlooked in pT1a RCC patients. Although this is a retrospective study, it focused on a homogeneous group of patients with pT1a RCC and the results were strengthened by the fact that all the pathological slides were reviewed by an experienced pathologist. Tumor size, grade, and stage are generally accepted to be prognostic factors, but several studies have reported that these factors had no effect on patients with low stage, small RCC [25,26]. In this study, there was no correlation between these features and distant metastasis.

Our study indicates that only 2 pathological features, microvascular invasion and tumor necrosis, are strong and independent predictors of distant metastasis. Microvascular invasion and tumor necrosis in patients with pT1a RCC who are undergoing surgery suggest they have more aggressive disease, and this calls for a closer follow-up.

CONCLUSIONS

In this study, microvascular invasion and tumor necrosis were the prognostic factors in patients with pT1a RCC. Classifying and evaluating patients on the basis of these pathological features may result in individualized follow-up schedules and better treatment for patients with pT1a RCC.

Conflicts of Interest
The authors have nothing to disclose.

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