

Urological Oncology

Factors Affecting the Time to Recurrence After Radical Nephrectomy for Localized Renal Cell Carcinoma

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Purpose: The objective of this study was to determine the factors affecting the time to recurrence after radical nephrectomy for localized renal cell carcinoma.

Materials and Methods: We retrospectively evaluated 321 patients who received radical nephrectomies for localized renal cell carcinoma (pT1a-pT2b N0M0). Of 29 patients with disease recurrence, 9 had recurrence more than 5 years after radical nephrectomy. We evaluated the clinicopathological factors, with the use of a retrospective study design.

Results: Tumor necrosis was statistically different between the late recurrence group and the recurrence free group (Fisher exact test, $p=0.046$). Hematuria at diagnosis (chi-square test, $p=0.045$) was statistically significant in early recurrence. In the univariate logistic regression analysis, tumor necrosis (odds ratio [OR], 4.629; 95% confidence interval [CI], 1.106 to 19.379; $p=0.036$) and pT stage > 1 (OR, 7.232; 95% CI, 1.727 to 30.280; $p=0.007$) were risk factors of late recurrence. In the multivariable logistic regression analysis, pT stage > 1 (OR, 7.143; 5% CI 1.706 to 29.912, $p=0.007$) was associated with late recurrence. Regarding early recurrence, initial symptoms at diagnosis and pathologic T stage > 1 were statistically significant in both univariate and multivariable logistic regression analysis. In terms of recurrence site, patients with late recurrence tended to have unusual metastasis sites other than lung, liver or bone (chi-square test, $p=0.012$).

Conclusions: These data suggest that tumor necrosis may affect late disease recurrence. Patients with initial symptoms and hematuria at diagnosis are vulnerable to recurrence in a shorter period after nephrectomy. Patients with late recurrence showed a tendency to have unusual metastasis site other than lung, liver or bone.

Keywords: Disease-free survival; Recurrence; Renal cell carcinoma

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INTRODUCTION

Worldwide, over 200,000 new cases of kidney cancer are diagnosed and approximately 100,000 deaths occur from this disease each year. Renal cell carcinoma (RCC) constitutes up to 85% of renal malignancies in adults. Despite the established role of radical or partial nephrectomy as a standard of treatment, a fair number of patients with localized tumors, ranging from 20% to 40%, will experience disease relapse [1]. In patients with recurrent RCC, the clinical course can vary, and survival can be stratified by an ob-

jective parameter called the memorial sloan-kettering cancer center risk score, which includes time to recurrence, lactate dehydrogenase, hemoglobin, corrected calcium, and performance status. However, limited information is available on clinical characteristics, prognostic factors, and outcomes in patients with late-recurring RCC [2,3]. In this study, we evaluated patients with disease recurrence after radical nephrectomy with respect to clinicopathological characteristics and focused on determining the predictive factors affecting different cancer-free intervals.

MATERIALS AND METHODS

1. Patients

From January 1990 to May 2012, a total of 363 patients underwent radical or partial nephrectomy for RCC with curative intent at Kyung Hee University Medical Center. We retrospectively evaluated 321 patients who underwent radical nephrectomy for clinically localized RCC. We defined clinically localized RCC as pathologically proven RCC of T stage 1a-2b without lymph node enlargement or metastasis at diagnosis. The pathologic stage was reassigned according to the 2009 Union Internationale Contre le Cancer and the American Joint Committee on Cancer TNM staging system. Histological subtypes were determined according to the Heidelberg classification of renal tumors. Tumor cell differentiation was assessed according to Fuhrman grading system. Patients were generally followed every 3 to 6 months for the first 2 years following surgery, every 6 months from the 3rd through the 5th year, and annually thereafter. Follow-up evaluation consisted of history taking, physical examination, routine blood tests with serum metabolic panels, and imaging evaluation. Abdomen and chest computerized tomography scans, bone scintigraphy, and brain imaging were conducted in clinically indicated cases. Unscheduled evaluations were done when the patient presented with symptoms suspicious of cancer recurrence. Disease recurrence was defined as tumor relapse according to the radiographic evidence. Cause of death (cancer-specific death) was determined by chart review or death certificate. Of 321 patients who underwent radical nephrectomy for localized RCC, 29 patients experienced recurrence. These patients were divided into two groups according to the recurrence-free period after nephrectomy. Patients who were diagnosed with recurrence within 5 years after radical nephrectomy (n=20) were grouped into the 'early recurrence' group. Patients with recurrence more than 5 years after radical nephrectomy (n=9) were included into the 'late recurrence' group. Mean recurrence-free survival was 22.1 months (range, 1 to 56 months) in the early recurrence group and 113.3 months (range, 64 to 166 months) in the late recurrence group. Among 292 patients without disease recurrence, 95 patients with more than 5 years of follow-up were enrolled as a control group. The mean follow-up period for the control group patients was 114.1 months (range, 61 to 237 months).

2. Statistical analysis

In comparing demographics and clinicopathological data among the three groups, analysis of variance was used for continuous variables and post hoc analysis was conducted with Bonferroni method. Chi-square test or Fischer exact test was used for categorical variables. Logistic regression analysis was applied to define clinicopathological factors affecting time to recurrence after radical nephrectomy. Data were analyzed by using IBM SPSS ver. 20.0 (IBM Co., Armonk, NY, USA). Reported p-values are two sided and

$p < 0.05$ was considered statistically significant.

RESULTS

1. Comparison among recurrence-free vs. early recurrence vs. late recurrence

Of a total of 321 patients who underwent radical nephrectomy for localized RCC, 29 patients were diagnosed with cancer recurrence. Of these, 20 patients (6.1%) were diagnosed with recurrence within 5 years after radical nephrectomy (early recurrence) and 9 patients (2.8%) were diagnosed with recurrence more than 5 years after radical nephrectomy (late recurrence). Tables 1, 2 list the demographic and histopathological characteristics of the three patient groups. According to our data, there were no significant differences in age, gender, body mass index, or histological subtypes among the three groups. Tumor necrosis was statistically significantly different between the late recurrence group and the recurrence-free group (Fisher exact test, $p=0.046$). On the other hand, tumor necrosis was not significant in the early recurrence group (Fisher exact test, $p=0.113$). Hematuria at presentation (chi-square test, $p=0.045$) was statistically significantly different between the early recurrence group and the recurrence-free group but was not significant in the late recurrence group. Fuhrman grade (Fisher exact test, $p=0.012$), tumor size, and pT stage were statistically significant in both the early (Fuhrman grade: Fisher exact test, $p=0.021$; tumor size: Bonferroni test, $p=0.001$; T stage: Fisher exact test, $p < 0.001$) and late (Fuhrman grade: Fisher exact test, $p=0.046$; tumor size: Bonferroni test, $p=0.006$; T stage: Fisher exact test, $p=0.002$) recurrence groups compared with the recurrence-free group. However, there was no statistically significant difference in any clinicopathological variables between the early and late recurrence groups.

2. Risk factors affecting recurrence after radical nephrectomy

In the univariate logistic regression analysis, tumor necrosis (odds ratio [OR], 4.629; 95% confidence interval [CI], 1.106 to 19.379, $p=0.036$) and pT stage > 1 (OR, 7.232; 95% CI, 1.727 to 30.280; $p=0.007$) were risk factors of late recurrence. In multivariable logistic regression analysis, pT stage > 1 (OR, 7.143; 95% CI, 1.706 to 29.912; $p=0.007$) was associated with late recurrence. Regarding early recurrence, initial symptoms at diagnosis (univariate analysis [OR, 3.414; 95% CI, 1.262 to 9.238; $p=0.016$], multivariable analysis [OR, 3.609; 95% CI, 1.298 to 10.032; $p=0.014$]) and pT stage > 1 (univariate analysis [OR, 3.115; 95% CI, 1.058 to 9.172; $p=0.039$], multivariable analysis [OR, 2.920; 95% CI, 1.028 to 8.298; $p=0.044$]) were statistically significant in both the univariate and multivariable logistic regression analyses (Table 3).

3. Analysis of sites of recurrence

The sites of recurrence were diverse, and we found a pre-

TABLE 1. Demographic and clinical characteristics of the patients

Variable	Recurrence-free (n=95)	Early recurrence ^a (n=20)	Late recurrence ^b (n=9)	p-value ^c
Age (y)	54.76±10.9	58.90±10.1	55.44±8.7	1.000
Gender				0.718
Male	62 (65.3)	11 (55.0)	5 (55.6)	
Female	33 (34.7)	9 (45.0)	4 (44.4)	
Body mass index (kg/m ²)	24.94±3.9	24.24±5.7	23.89±3.8	1.000
Mass-induced symptoms ^d				0.687
Present	23 (24.2)	8 (40.0)	3 (33.3)	
Absent	72 (75.8)	12 (60.0)	6 (66.7)	
Evidence of hematuria at diagnosis ^e				0.813
Absent	73 (76.8)	11 (55.0)	7 (77.8)	
Microscopic hematuria	15 (15.8)	4 (20.0)	1 (11.1)	
Gross hematuria	7 (7.4)	5 (25.0)	1 (11.1)	

Values are presented as mean±standard deviation or number (%).

^a:Recurrence with metastasis less than 5 years after radical nephrectomy. ^b:Recurrence with metastasis more than 5 years after radical nephrectomy. ^c:For late recurrence vs. recurrence-free group. ^d:Flank pain, abdominal discomfort, palpable mass. ^e:p < 0.05, for early recurrence vs. recurrence-free group.

TABLE 2. Histopathological characteristics of the patients

Variable	Recurrence-free (n=95)	Early recurrence (n=20)	Late recurrence (n=9)	p-value ^a
Tumor size (cm) ^b	4.39±2.6	6.85±3.3	7.44±2.7	0.006
Pathological stage ^b				0.002
pT1a	59 (62.1)	3 (15.0)	1 (11.1)	
pT1b	22 (23.2)	10 (50.0)	3 (33.3)	
pT2a	12 (12.6)	4 (20.0)	3 (33.3)	
pT2b	2 (2.1)	3 (15.0)	2 (22.2)	
Histological subtype				0.542
Clear cell	78 (82.1)	20 (100.0)	8 (88.9)	
Papillary	4 (4.2)	0 (0)	1 (11.1)	
Chromophobe	10 (10.5)	0 (0)	0 (0)	
Others	3 (3.2)	0 (0)	0 (0)	
Fuhrman grade ^b				0.046
G1	9 (9.5)	0 (0)	0 (0)	
G2	40 (42.1)	3 (15.0)	2 (22.2)	
G3	20 (21.1)	7 (35.0)	1 (11.1)	
G4	2 (2.1)	2 (10.0)	2 (22.2)	
Unknown	24 (25.3)	8 (40.0)	4 (44.4)	
Sarcomatoid differentiation				1.000
Present	0 (0)	1 (5.0)	0 (0)	
Absent	95 (100)	19 (95.0)	9 (100)	
Tumor necrosis ^c				0.046
Present	14 (14.7)	6 (30.0)	4 (44.4)	
Absent	81 (85.3)	14 (70.0)	5 (55.6)	

Values are presented as mean±standard deviation or number (%).

^a:For late recurrence vs. recurrence-free group. ^b:p < 0.05, for early recurrence vs. recurrence-free group. ^c:Tumor necrosis: coagulative necrosis under microscopic 400 times magnification.

dominance of unusual sites, other than lung, liver, or bone, in the late recurrence group (chi-square test, p=0.012; Table 4). Of a total of 29 patients with recurrence, 6 patients (30.0%) and 3 patients (33.3%) had multiple sites of metastasis in the early and late recurrence groups, respectively. In the early recurrence group, lung (n=11, 36.7%) was the most frequent site of recurrence, followed by bone (n=7,

23.3%), liver (n=4, 13.3%), lymph node (n=3, 10.0%), muscle (n=2, 6.67%), contralateral kidney (n=1, 3.3%), spleen (n=1, 3.3%), and peritoneum (n=1, 3.3%). In the late recurrence group, lung was also the most frequent organ of recurrence (n=6, 28.6%). On the other hand, more diverse distribution of metastasis was observed in the late recurrence group: brain (n=3, 14.3%), contralateral kidney

TABLE 3. Logistic regression analysis of factors associated with early recurrence and late recurrence

Factor	Early recurrence ^a				Late recurrence ^b			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Initial symptom	3.414 (1.262-9.238)	0.016	3.609 (1.298-10.032)	0.014	2.845 (0.712-11.369)	0.139		
pT > 1	3.115 (1.058-9.172)	0.039	2.920 (1.028-8.298)	0.044	7.232 (1.727-30.280)	0.007	7.143 (1.706-29.912)	0.007
Clear cell type					1.641 (0.192-14.050)	0.651		
Fuhrman nuclear grade 3-4	2.715 (0.997-7.392)	0.051			1.659 (0.383-7.184)	0.498		
Tumor necrosis	2.480 (0.816-7.539)	0.109			4.629 (1.106-19.379)	0.036		

Multivariate logistic regression analysis after backward stepwise elimination with variables eliminated at p < 0.1. OR, odds ratio; CI, confidence interval.

^a:Recurrence with metastasis less than 5 years after radical nephrectomy. ^b:Recurrence with metastasis more than 5 years after radical nephrectomy.

TABLE 4. Site of recurrence and clinical information associated with recurrence by patient group

Variable	Early recurrence	Late recurrence	p-value
No. of sites			1.000
Single site	14 (70.0)	6 (66.7)	
Multiple	6 (30.0)	3 (33.3)	
Site of recurrence ^a			0.012 ^c
Lung	11 (36.7)	6 (28.6)	
Liver	4 (13.3)	1 (4.8)	
Bone	7 (23.3)	1 (4.8)	
Other site ^b	8 (26.7)	13 (61.9)	
Symptoms related to metastasis			0.694
Present	7 (35.0)	4 (44.4)	
Absent	13 (65.0)	5 (55.6)	

Values are presented as number (%).

^a:Some patients had more than one recurrent site. ^b:Other site: lymph node, brain, pancreas, gall bladder, stomach, duodenum, colon, muscle, contra-lateral kidney, spleen, peritoneum, pleura.

^c:Chi-square test in comparison of 'other sites' with 'lung, liver or bone.'

(n=2, 9.5%), pancreas (n=1, 4.8%), gall bladder (n=1, 4.8%), stomach (n=1, 4.8%), colon (n=1, 4.8%), duodenum (n=1, 4.8%), pleura (n=1, 4.8%), muscle (n=1, 4.8%), lymph node (n=1, 4.8%), liver (n=1, 4.8%), and bone (n=1, 4.8%).

DISCUSSION

Disease recurrence in patients with localized RCC after curatively intended radical nephrectomy can occur at any time. However, late recurrence after radical nephrectomy is not common. The definition of 'late recurrence' in RCC is not clearly established. The reason we determined 5

years as a cutoff value was because surveillance patterns change at 5 years after curative treatment for RCC [4]. Also, some have suggested that surveillance after 5 years is no longer necessary for cost-effectiveness in low-risk patients [3,4]. Nevertheless, about 10% to 20% of patients with disease recurrence develop late recurrence more than 5 years after nephrectomy [2]. The final objective of our study was to determine the risk factors predictive of late recurrence, at the point of radical nephrectomy, which could thus be incorporated into the postoperative surveillance guideline. In our studies, of a total of 104 patients with follow-up for more than 5 years after radical nephrectomy for localized RCC, 9 patients (9.1%) developed late recurrence. To date, several studies have been conducted to determine the differential characteristics of late recurrence of localized RCC after radical nephrectomy. However, on the basis of the current medical literature, no consensus has been reached about the parameters predicting late recurrence of localized RCC because of the small patient numbers [2-16]. According to the study by Adamy et al. [3], which was conducted with 44 patients with late recurrence (beyond 5 years after nephrectomy), patients with late recurrence tended to have fewer initial symptoms, smaller tumor size, and less aggressive disease (pT1) compared with patients with early recurrence. Adamy et al. [3] also suggested that patients with late recurrence tend to be in an MSKCC favorable risk group. Park et al. [5] evaluated 41 patients with late recurrence (beyond 5 years after nephrectomy) and suggested that old age and high high-sensitivity C-reactive protein levels at the time of operation were independent predictive factors for late recurrence. Brookman-May et al. [2] studied a total of 310 patients with cancer recurrence more than 5 years after radical nephrectomy and compared the characteristics of these patients with recurrence-free patients. They proved that lymphovascular invasion, Fuhrman grade 3-4, and pT

stage > pT1 were significantly associated with late recurrence. Ha et al. [6] evaluated 14 patients with disease recurrence more than 5 years after radical or partial nephrectomy among 423 patients with pathologically confirmed stage T1 clear cell RCC and showed that symptoms at diagnosis and pT stage were independent predictive factors for late recurrence. In the present study, unlike in previous studies, we tried to determine the factors that affected time to recurrence after radical nephrectomy and to discover the differential characteristics of patients in the early and late recurrence groups, respectively. We found that tumor necrosis was associated with late disease recurrence and initial clinical symptoms were associated with early recurrence. Large tumor size, advanced pathologic stage, and advanced Fuhrman nuclear grade were associated with both early and late recurrence. We also evaluated the correlation of tumor size and tumor necrosis in all the patients involved in this study. According to the logistic regression analysis, tumor size was shown to be a risk factor of tumor necrosis (OR, 1.261; 95% CI, 1.086 to 1.463; $p=0.002$).

Tumor necrosis was initially recognized in the 1970s as a predictor of aggressive RCC behavior [17]. Minervini et al. [18] confirmed that histological tumor necrosis is a statistically significant prognostic factor in patients with non-metastatic clear cell RCC. Kim et al. [7] suggested that the survival rate of patients with tumor necrosis was significantly lower than that of patients without tumor necrosis. According to the previously published medical literature, the definitions for tumor necrosis are diverse. However, most investigators have defined histological necrosis, as a prognostic factor, as the presence of any microscopic coagulative tumor necrosis, without consideration of degenerative changes such as hyalinization, hemorrhage, and fibrosis [17,18]. We also determined tumor necrosis as the presence of microscopic coagulative tumor necrosis. As we showed in Tables 2, 3, tumor necrosis was statistically significant only in the late recurrence group. In consideration of the hypothesis that rapid tumor cell growth outgrows its own blood supply and subsequently creates a hypoxic condition and resultant tumor necrosis, this result might be contradictory. However, in several recent reports, a high proliferation index or insufficient oxygen supply (hypoxia inducible factor-1, or HIF-1 α) and high Ki-67 (a proliferation marker) expression were not interchangeable with tumor necrosis. Some medical literature suggests that host immunologic factors, such as differential expression of chemokines, may be involved in tumor necrosis [19]. Although the exact nature of immunologic triggers and tumor necrosis remain to be clarified, there might be a kind of 'time-related function' between 'tumor necrosis' and a 'tumor dormancy state'.

This study also showed the diversity of the recurrence site in the late recurrence group. The lung, liver, and bone are known as the usual recurrence organs of malignant neoplasms, including RCC [20], and we found such a tendency in the early recurrence group. However, there was a predominance of cancer recurrence at other sites in the late

recurrence group, such as the lymph node, brain, pancreas, gall bladder, stomach, duodenum, colon, muscle, contralateral kidney, and pleura. The question of differences in metastasis site according to recurrence-free interval remains to be answered. Bruin et al. [21] suggested that organ-specific metastasis localization can be predicted by specific genomic aberrations in primary colorectal cancer [5]. Yerushalmi et al. [22] showed that cancer antigen 125 levels varied among the different sites of metastasis in breast cancer [5]. Koo et al. [23] reported that metastatic breast cancer showed different phenotypes of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 according to the different recurrence sites [5]. Therefore, understanding the molecular biological mechanisms underlying RCC might solve these questions.

The potential limitations of our study lie in its retrospective design. There was no standardized postoperative follow-up protocol and the quality of imaging modality has improved substantially during the past 30 years. No incorporation of molecular markers is another limitation of this study. Furthermore, the small number of patients who were evaluated in a single institution might have affected our study data. For this reason, we are planning to conduct a multicenter study with a large patient pool to minimize these biases.

CONCLUSIONS

This study suggested that the presence of microscopic coagulative necrosis in the resected specimen may be a predictive factor of late recurrence after radical nephrectomy for localized RCC. Also, clinical symptoms such as hematuria, flank pain, and a palpable mass at diagnosis may predict disease recurrence in a short period after radical nephrectomy. Large tumor size, advanced pathologic stage, and advanced Fuhrman nuclear grade may be risk factors for both early and late recurrence. Therefore, we suggest that patients with tumor necrosis may need to undergo long-term, thorough surveillance after radical nephrectomy for localized RCC.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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