

Predictive factors for disease recurrence in patients with locally advanced renal cell carcinoma treated with curative surgery

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Abstract

Background: Few prognostic factors have been proposed for patients with locally advanced renal cell carcinoma (RCC). This study aimed to investigate the possible predictive factors for disease-free survival (DFS) after curative surgery for RCC stage T3 or higher.

Methods: Patients with locally advanced RCC who underwent cure-intended partial or radical nephrectomy, with or without tumor thrombectomy, at our institution from April 1, 2005 to October 31, 2013 were retrospectively reviewed. Those undergoing cytoreductive nephrectomy were excluded. Preoperative data, including surgical and pathologic characteristics, were assessed for correlation with DFS. Chi-square tests, univariate and multivariate Cox regression analysis, and Kaplan–Meier survival curve analyses were performed to determine potential predictive factors. A *p* value less than 0.05 was considered statistically significant.

Results: A total of 159 patients were included for analysis. The mean duration of follow-up was 37.9 months, and 119 (74.8%) patients remained disease-free during follow-up. Disease recurrence was found in 40 (25.2%) patients, and pathologic T stage, capsule penetration, Fuhrman grade, thrombocytosis, renal vein thrombosis, and elevated serum alkaline phosphatase, platelet/lymphocyte ratio, and γ -glutamyl transpeptidase levels were significantly associated with disease recurrence on univariate analysis. On multivariate analysis, Fuhrman grade 3 or 4 (HR = 5.70, *p* = 0.0003, 95% CI = 2.23–14.56) showed significant associations with DFS.

Conclusion: In patients with locally advanced RCC, Fuhrman grade was associated with worse DFS after curative surgery. Urologists should closely monitor patients with high Fuhrman grades.

Keywords: Disease-free survival; Fuhrman grade; Prognosis; Renal cell carcinoma

1. INTRODUCTION

Renal cell carcinoma (RCC) is the sixth most common cancer in men, and the ninth most common cancer in women, worldwide.¹ The incidence is approximately 12 per 100 000 persons per year.^{1,2} Since most patients with RCC are asymptomatic, about one-third of patients are diagnosed at a late stage.¹

Radical nephrectomy, with or without thrombectomy, and partial nephrectomy for highly selected cases, are the only curative treatments for patients with locally advanced RCC without

distal metastases.³ There are several prognostic models to predict the treatment response in localized RCC.^{4–6} However, few prognostic factors have been proposed specifically for patients with locally advanced RCC.^{7,8}

In this study, we investigated the possible predictive factors for disease-free survival after surgery (DFS) for RCC stage T3 or higher. To the best of our knowledge, this is the first study evaluating the predictive factors of disease recurrence in patients with locally advanced RCC.

2. METHODS

We conducted the present research according to the Declaration of Helsinki and the principles of research ethics of our institutional review board. However, the review process by the committee was not mandatory since this was a retrospective, pure chart review study.

Patients with locally advanced RCC who underwent cure-intended partial or radical nephrectomy, with or without tumor thrombectomy, at our institution from April 1, 2005 to October 31, 2013 were retrospectively recruited from our medical database. Those participating in clinical trials of adjuvant targeted therapy after nephrectomy were also included. The locally advanced RCC was defined as RCC staging T3 or greater

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Table 1
Demographic data of patients with locally advanced renal cell carcinoma (n = 159)

Variables	N	(%)
Sex		
Female	49	(30.8)
Male	110	(69.2)
Age		
≤ 65 years	92	(57.9)
> 65 years	67	(42.1)
Tumor location		
Right	72	(45.3)
Left	86	(54.1)
Bilateral	1	(0.6)
Open or laparoscopic surgery		
Open surgery	111	(69.8)
Laparoscopic surgery	48	(30.2)
Radical or partial nephrectomy		
Radical surgery	117	(73.6)
Partial surgery	42	(26.4)
Pathology T stage (AJCC 7th edition)		
T3a	134	(84.3)
T3b	14	(8.8)
T3c	7	(4.4)
T4	4	(2.5)
Renal cell carcinoma type		
Clear cell	129	(81.1)
Chromophobe	14	(8.8)
Papillary	13	(8.2)
Collecting duct	1	(0.6)
Xp11.2 translocation	2	(1.3)
Fuhrman grade		
1	1	(0.7)
2	62	(44.0)
3	57	(40.4)
4	21	(14.9)
Necrosis		
Absent	46	(30.5)
Focal	77	(51.0)
Extensive	28	(18.5)
Capsule penetration		
No	109	(69.9)
Yes	47	(30.1)
Hilar vein involvement		
No	57	(36.3)
Yes	100	(63.7)
Positive surgical margin		
No	97	(93.3)
Yes	7	(6.7)
Sinus fat invasion		
No	57	(37.8)
Yes	94	(62.3)
Muscular branch involvement		
No	68	(44.2)
Yes	86	(55.8)
Sarcomatoid differentiation		
No	149	(93.7)
Yes	10	(6.3)
Lymphadenopathy		
No	144	(92.3)
Yes	12	(7.7)
BMI > 25		
No	64	(52.5)
Yes	58	(47.5)

Continued next page

Table 1 (Continued)

Variables	N	(%)
Postoperative complication		
No	135	(84.9)
Yes	24	(15.1)
Adjuvant targeted therapy		
No	136	(86.1)
Yes	22	(13.9)
Disease recurrence		
No	119	(74.8)
Yes	40	(25.2)
Disease-free survival (mo)	33.0 ± 26.8	

AJCC = American Joint Committee on Cancer; BMI = body mass index.

according to 7th American Joint Committee on Cancer. Patients with known metastases and those who underwent cytoreductive nephrectomy were excluded. Preoperative data, including patient demographics, biochemical data, and surgical and pathologic characteristics were collected. Patients underwent follow-up chest radiography, abdominal computed tomography, and whole-body bone scans every 3 months for the first 2 years after surgical intervention, or as indicated in cases of newly-developed symptoms. The follow-up interval was extended if no recurrence developed after 2 years. Those without local recurrence or distant metastases were classified as disease-free during follow-up.

Chi-square test of categorical variables was performed. Significant variables on chi-square test were extracted for further evaluation on univariate and multivariate analyses. Univariate and multivariate Cox regression, and Kaplan–Meier survival curve analyses were performed to determine these predictive factors of DFS. Statistical analyses were performed using Statistical Analysis Software, Version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). A *p* value less than 0.05 was considered as statistically significant.

3. RESULTS

A total of 159 patients were included for analysis (110 [69.2%] male and 49 [30.8%] female). The mean age at surgery was 62.2 years (SD, 15.3 years). **Table 1** shows the characteristics of the patient cohort. The mean duration of follow-up was 37.9 months (SD, 27.9 months). One hundred nineteen patients (74.8%) remained disease-free during the postoperative follow-up. The mean DFS was 33.0 months (SD, 26.8 months). Forty patients (25.2%) developed disease recurrence, including distant metastasis in 37 and local recurrence in 17 patients.

Table 2 shows the possible predictive factors for disease recurrence according to the chi-square tests. In brief, a pathologic stage higher than pT3a, Fuhrman grade of 3 or 4, presence of capsule penetration, renal vein thrombosis, thrombocytosis, and elevated platelet/lymphocyte ratio, alkaline phosphatase (alk-p), and γ -glutamyl transpeptidase (rGT) levels were significantly associated with disease recurrence. Age, sex, blood type, surgical method, perioperative blood transfusion, RCC cell type, positive surgical margin (PSM), presence of sarcomatoid differentiation, and adjuvant targeted therapy failed to reach statistical significance.

Table 3 revealed the result of univariate and multivariate cox regression analysis. On univariate Cox regression analysis, pathologic stage higher than pT3a, renal vein thrombosis, thrombocytosis, capsule penetration, high Fuhrman grade, and elevated serum alk-p levels had significant associations with DFS and were included for multivariate analysis. On multivariate Cox regression analysis, only Fuhrman grade 3 or 4 (HR = 5.70, *p* = 0.0003, 95% CI = 2.23–14.56) showed significant associations with DFS. The Kaplan–Meier survival curve for Fuhrman grade is illustrated in Fig. 1.

Table 2
Possible predictor of disease recurrence in patients with locally advanced renal cell carcinoma

Variables	Disease recurrence		p
	No (n = 119)	Yes (n = 40)	
Male sex	80 (67.23)	30 (75.00)	0.357
Age > 65 years	50 (42.02)	17 (42.50)	0.957
BMI > 25 kg/m ²	47 (51.65)	11 (35.48)	0.120
Laparoscopic surgery	37 (31.09)	11 (27.50)	0.669
Partial nephrectomy approach	36 (30.25)	6 (15.00)	0.058
Pathology T stage (AJCC 7th edition) > T3a	11 (9.24)	14 (35.00)	<0.001
Stage upward migration after surgery	53 (55.21)	18 (50.00)	0.593
Fuhrman grade 3 or 4	48 (47.46)	30 (78.95)	0.001
Clear cell type	99 (83.19)	30 (75.00)	0.252
Presence of extensive necrosis	17 (15.18)	11 (28.21)	0.071
Presence of renal vein thrombosis	11 (9.24)	13 (32.50)	0.0004
Presence of capsule penetration	28 (23.93)	19 (48.72)	0.004
Positive surgical margin	5 (5.95)	2 (10.00)	0.516
Sarcomatoid differentiation	5 (4.20)	5 (12.50)	0.123
Presence of lymphadenopathy	6 (5.08)	6 (15.79)	0.072
Type O blood	51 (42.86)	15 (37.50)	0.552
Perioperative blood transfusion	6 (26.09)	8 (47.06)	0.169
Preoperative leukocytosis	2 (1.75)	3 (7.50)	0.111
Preoperative thrombocytosis	10 (8.40)	10 (25.00)	0.006
Platelet/lymphocyte ratio <130	57(50.00)	12(30.00)	0.029
Preoperative anemia	62 (52.10)	27 (67.50)	0.090
Preoperative hematuria	40 (33.61)	10 (25.64)	0.353
Hypercalcemia	1 (0.87)	0 (0.00)	1.000
Elevated serum creatinine	13 (10.92)	3 (7.50)	0.763
Elevated serum alkaline phosphatase (alk-p)	13 (11.30)	9 (25.71)	0.035
Elevated serum lactate dehydrogenase	17 (14.66)	9 (25.00)	0.150
Elevated serum alanine transaminase	12 (10.08)	6 (15.00)	0.397
Elevated serum aspartate transaminase	4 (3.42)	2 (5.26)	0.635
Elevated serum γ -glutamyl transpeptidase	8 (7.34)	7 (20.59)	0.049
Perioperative complications	20 (16.81)	4 (10.00)	0.298
Adjuvant targeted therapy	13 (11.02)	9 (22.50)	0.070

Data are presented as number (percentage).

Red font indicates statistical significance ($p < 0.05$).

AJCC = American Joint Committee on Cancer; BMI = body mass index.

4. DISCUSSION

There are several prognostic systems and nomograms to predict survival after nephrectomy for RCC.^{4-6,9-11} However, these systems include RCCs of all stages, rather than focusing on locally advanced RCC, which is technically challenging for urologists, with a potentially different prognostic factor compared to that for early-stage disease. In the present study, we found that locally advanced RCC with capsule penetration was significantly associated with recurrence after curative surgery, whilst a PSM, a pathologic T stage higher than T3a, administration of adjuvant targeted therapy, and elevated preoperative liver function test results were not significantly related to disease recurrence.

In the present study, higher Fuhrman grade was an independent predictive factor for DFS in patients with locally advanced RCC treated with curative surgery. The Fuhrman grade is a well-known predictor for disease progression, not only in early-stage RCC, but also in locally advanced RCC.^{12,13} For example, in a study utilizing data from a Chinese database, a modified Fuhrman grade of 3 or 4 was one of the independent predictive factors for postoperative cancer-specific survival (CSS) ($p = 0.001$, HR = 5.194) in patients with locally advanced RCC.¹⁴ Additionally, Schiavina *et al.* reported that a higher Fuhrman grade was an independent predictor for CSS in T3a RCC.¹⁵ Thus, the present study, along with previous studies, suggests

that higher Fuhrman grade is associated with a poor prognosis in patients with locally advanced RCC.

Interestingly, elevated preoperative liver function markers, including alk-p and rGT, were associated with disease recurrence in the univariate, but not multivariate, analyses in the present study. In a systematic review from 2014, the alk-p level was reported as a promising biomarker for the detection of bony metastases in patients with malignancy.¹⁶ However, the usefulness of alk-p in RCC remains controversial.

Kattan *et al.*¹⁷ developed a nomogram incorporating elevated alk-p to predict 12-month progression-free survival in patients with advanced RCC treated with pazopanib. A similar prognostic model to stratify advanced RCC into different risk groups according to elevated alk-p and other clinical parameters were also proposed by Amato *et al.*¹⁸ Furthermore, in a large retrospective study of 2945 patients with RCC who underwent radical nephrectomy for a cure, Margulis *et al.*¹⁹ reported that elevated alk-p had a negative influence on CSS in patients with local recurrence. On the other hand, Jung *et al.*²⁰ found that it was difficult to diagnose bone metastasis using turnover markers, including alk-p, in 72 patients with localized and metastatic RCC. Elevated serum alk-p might be an indicator of micrometastasis in the bone that cannot be detected using current image modalities. Another possible explanation for the conflicting results is the presence of nonmetastatic hepatic dysfunction, also known as Stauffer syndrome. It is estimated that this syndrome develops in 13.2% of patients with RCC.²¹ Stauffer syndrome is believed to be associated with higher levels of inflammatory interleukin-6, and imply a poor prognosis.^{21,22} In another similar retrospective study, paraneoplastic syndrome was one of the independent predictive factors for CSS.¹⁴ The manifestations of this paraneoplastic syndrome, including elevated serum alk-p and rGT, and thrombocytosis, were also correlated with disease recurrence in the univariate analyses of the present study. Further prospective studies that include more patients are warranted to determine the prognostic significance of these clinical parameters in patients with locally advanced RCC before surgical intervention.

PSM is often considered a poor prognostic factor for malignancy;²³⁻²⁵ however, this remains debatable for RCC. Several studies have shown that PSM has little impact on RCC survival or recurrence.²⁶⁻²⁸ PSM does not necessarily indicate residual tumor tissue inside the patient's body. The residual tumor tissue may be too close to the margin to be destroyed during resection with electrocauterization. Moreover, surgery may disturb the blood supply to the residual tumor cells inside the patient's body, and they may not survive after surgical intervention. Further studies are needed to clarify the association between PSM and disease recurrence in patients with locally advanced RCC.

Pathologic T stage is a well-known prognostic factor;^{6,10,29} however, it was not a prognostic factor in our locally advanced RCC series. For most malignancies, a higher T stage suggests a larger tumor size. However, locally advanced RCC is unique compared to other cancers, as a T stage higher than T3 is defined according to its location inside the kidney, as well as its relationships with adjacent structures, especially the great vessels. To perform curative surgery for an RCC higher than T3a is typically demanding, as it usually involves the inferior vena cava, requiring cooperation between urologists and vascular surgeons. It is possible that a selection bias was responsible for the insignificance of T stage found in the present study.

The present study was several limitations. First, this was a retrospective study of data from a single center, involving several urologists. The impact of an individual urologist's surgical skills on disease recurrence is hard to clarify. Nevertheless, there was no statistical significance in DFS rates between the different urologists at our institution. Second, there a high proportion of

Table 3

Univariate and multivariate Cox regression analysis of predictive factors for disease recurrence in patients with locally advanced renal cell carcinoma treated with curative surgery

Variables	Univariate Cox regression		p	Multivariate Cox regression		p
	HR	(95% CI)		HR	(95% CI)	
Pathology T stage						
T3a	1			1		
>T3a	3.97	(2.06, 7.68)	<0.0001	1.87	(0.53, 6.56)	0.329
Fuhrman grade						
1 and 2	1			1		
3 and 4	3.76	(1.72, 8.22)	0.001	5.70	(2.23, 14.56)	0.0003
Capsule penetration						
No	1			1		
Yes	2.52	(1.34, 4.72)	0.004	1.67	(0.81, 3.42)	0.163
Renal vein thrombosis						
No	1			1		
Yes	4.04	(2.08, 7.85)	<0.0001	2.72	(0.83, 8.88)	0.098
Thrombocytosis						
No	1			1		
Yes	2.95	(1.44, 6.05)	0.003	2.55	(0.90, 7.22)	0.078
Platelet/lymphocyte ratio <130						
No	1			1		
Yes	0.51	(0.26, 1.01)	0.053			
Elevated alk-p						
No	1			1		
Yes	2.18	(1.02, 4.67)	0.044	1.03	(0.36, 2.98)	0.951
Elevated rGT						
No	1			1		
Yes	2.23	(0.96, 5.14)	0.061			

Red font indicates statistical significance ($p < 0.05$).

AJCC = American Joint Committee on Cancer; CI = confidence interval; HR = hazard ratio; rGT = serum γ -glutamyl transpeptidase; alk-p = serum alkaline phosphatase.

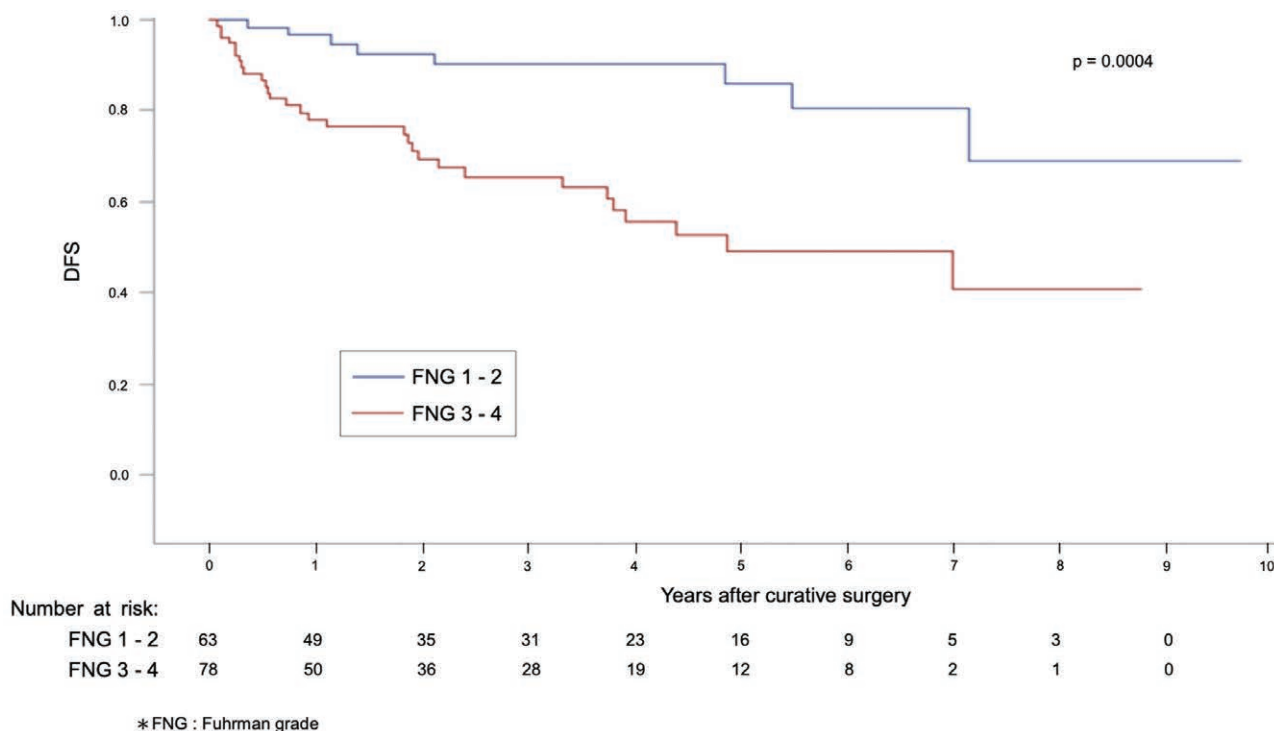


Fig. 1 The Kaplan-Meier curves for disease-free survival (DFS) according to Fuhrman grade (FNG).

patients with T3a RCC in our patient cohort. This may have been due to the detailed examination of the specimens performed by the pathologists at our institution. Some T1 and T2 RCCs were upstaged to T3a when tumor involvement of segmental blood vessels or perinephric fat was detected. The present study findings are still valuable because very few studies have focused on the Asian population. Moreover, to the best of our knowledge, this is the first study investigating the prognosis of patients with locally advanced RCC treated with curative nephrectomy. Because of the high risk of disease recurrence and progression, the exploration of prognostic factors can aid in risk stratification, patient counseling, postoperative follow-up, and the decision to administer adjuvant immunotherapy.

In conclusion, in patients with locally advanced RCC, the presence of a high Fuhrman grade can predict shorter DFS after curative surgery. Urologists should monitor such patients closely and carefully. Moreover, the development of a nomogram for patients with locally advanced RCC to stratify the risk of disease recurrence may be helpful in clinical practice.

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