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Prognostic Evaluation of the Site of Invasion in Pathological Stage T3a Renal Cell Carcinoma

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Abstract. *Background/Aim: To investigate the prognostic values of fat invasion (FI) and renal vein invasion (RVI) in pT3a renal cell carcinoma (RCC), as single factors or concomitant presence. Patients and Methods: We retrospectively reviewed the data of 173 patients who underwent radical or partial nephrectomy for RCC in our Institution. Results: At a median follow-up time of 48 months, patients with RVI showed significantly increased risk of disease recurrence and worse cancer-specific survival (CSS) when compared to those with FI (p=0.007, p=0.022, respectively). Having combined RVI and FI did not show inferior prognosis compared to those with RVI only. In multivariable analysis, RVI was an independent factor for disease recurrence (HR=2.06, 95% CI=1.10-3.87, p=0.024) and CSS (HR=2.46, 95% CI=1.01-6.0, p=0.048). Conclusion: For patients with T3a renal tumors, RVI was associated with inferior prognosis compared to those with FI.*

Tumor staging is a process for determining the severity of the primary tumors and the condition of its extension. It helps predict prognosis, make disease management plans and formulate surveillance strategies. In the recent 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system, T3a renal cell carcinoma (RCC) was defined as a tumor with renal vein invasion (RVI), pelvicalyceal system invasion (PSI), perirenal fat invasion (PFI) or sinus fat invasion (SFI) (1).

Theoretically, patients with renal tumors at the same stage should experience similar disease recurrence and survival rates. However, previously published literature reported that the oncologic outcomes regarding the different extrarenal extension sites in pathological stage T3a RCC are heterogeneous and further studies to investigate these differences were necessary (2-9).

In the present study, we aimed to evaluate the impact surrounding different sites of extrarenal invasion on one's prognosis in pT3a RCC, as well as the effect of tumor size for these patients.

Patients and Methods

Following the Institutional Review Board's approval, a retrospective chart review of patients who had undergone radical or partial nephrectomy for renal tumors between 2000 and 2018 was performed at our Hospital. Renal tumors diagnosed as pathological stage T2 and T3 RCC pathologically were included. All patients received pre-operative, cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) for accurate tumor staging. Regional lymph node dissection was performed if the patient was found to have enlarged lymph nodes discovered during preoperative image studies. Patients with metastatic disease and inadequate data for analysis were excluded from analysis.

According to tumor stages and site of invasion, we divided patients into 4 groups: T2, T3a with fat invasion (FI), T3a with RVI and T3b+T3c. The T2 and T3b+T3c groups were used to compare and investigate if the prognosis of the T3a cohorts were similar to the groups below or above the T3a.

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Key Words: Fat invasion, pathological T3a, prognosis, renal cell carcinoma, renal vein invasion.

Table I. *Patient demographics, pathological characteristics and outcomes.*

	T2 (n=47)	T3a FI (n=71)	T3a RVI (n=36)	T3b+T3c (n=19)	*p*-Value
Age, years (IQR)	52 (41-69)	60 (51-72)	63.5 (53.8-72.8)	55 (40-73)	0.145
Male Gender, n (%)	25 (53.1)	46 (64.8)	26 (72.2)	11 (57.9)	0.319
Follow up, months (IQR)	71 (31-112)	51 (24-72)	45.5 (17-78)	18 (12-33)	<0.001*
Tumor size, cm (IQR)	8.5 (7.6-10)	6.5 (4.5-9)	7 (5.8-9)	8 (6-10)	<0.001*
Fuhrman grade, n (%)					0.176
1	0	1	0	0	
2	12	25	8	4	
3	16	25	10	7	
4	4	14	7	4	
unknown	15	6	11	4	
Histology, n (%)					
Clear	24	53	26	9	<0.001*
Papillary	5	5	0	5	
Chromophobe	15	4	3	0	
Others	3	9	7	5	
Necrosis, n (%)	22 (46.8)	23 (32.4)	11 (30.6)	12 (63.2)	0.042*
Sarcomatoid festures, n (%)	1 (2.1)	6 (8.4)	2 (5.6)	5 (26.3)	0.011*
LVI, n (%)	4 (8.5)	13 (18.3)	18 (50)	14 (73.7)	<0.001*
Margin Positive, n (%)	0	2 (2.8)	4 (11.1)	1 (5.2)	0.073
Partial Nephrectomy, n (%)	5 (10.6)	10 (14.0)	1 (2.8)	0	0.021*
Recurrence, n (%)	14 (27.7)	21 (28.2)	19 (50.0)	1 (68.4)	0.003*
Local recurrence	0	3	1	0	
Distant metastasis	13	16	14	12	
Local recurrence+ distant metastasis	0	1	3	1	
CSS, n (%)	43 (91.5)	62 (83.8)	25 (69.4)	13 (68.4)	0.013*
OS, n (%)	43 (91.5)	55 (77.5)	23 (63.8)	12 (63.2)	0.011*

CSS: Cancer specific survival; FI: fat invasion; IQR: interquartile range; LVI: lymphovascular invasion; OS: overall survival; RVI: renal vein invasion. *Statistically significant *p*-values.

Patient demographics, clinicopathological and surgical characteristics were obtained and evaluated. Continuous variables were expressed as medians and interquartile range (IQR). The Kruskal-Wallis test was used to compare the means of continuous variables, while the Chi-square test was used to compare categorical variables. Recurrence free survival (RFS) and cancer specific survival (CSS) were estimated using the Kaplan-Meier method and compared using log-rank tests. Univariable and multivariable Cox proportional hazard regression models were used to identify the clinical and pathologic factors for prognosis. A p-value <0.05 was considered statistically significant, and all analyses were performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA).

Results

A total of 173 patients were included in the study. Patients were divided into 4 groups: T2 (n=47), T3a with FI (n=71), T3a with RVI (n=36) and T3b+T3c (n=19). Demographics, clinicopathological features and oncologic outcomes between the 4 groups were compared and are presented in Table I.

The median follow-up time was 48 months, during which 67 patients (38.7%) experienced disease recurrence at a median (IQR) of 10 (6-30) months, with patients in the T3a with RVI and T3b+T3c groups having a significantly higher risk of disease recurrence than the other 2 groups (p=0.003). Thirty patients (17.3%) died from disease progression at a median follow-up time (IQR) of 20.5 (14.5-37.3) months, with T3a with RVI and T3b+T3c groups having a significantly reduced cancer specific survival rate (p=0.013).

Survival analysis using the Kaplan-Meier method is shown in Figure 1. RFS was worst at the T3b+T3c group. The T3a with RVI group experienced significantly inferior RFS when compared to the T3a with FI group (p=0.007). Additionally, RFS for the T3a with FI group was similar to that of the T2 group (p=0.699). Similar results were also observed regarding CSS. The worst CSS was found in the T3b+T3c group, while the T3a with RVI group displayed significantly reduced CSS when compared to the T3a with FI group (p=0.022). The 5-year RFS was 74.8% for T2, 67.7% for T3a with FI, 42.2% for T3a with RVI and 14.1% for T3b+T3c. The 5-year CSS was 92.9% for T2, 85.6% for T3a with FI, 68.2% for T3a with RVI and 60.7% for T3b+T3c.

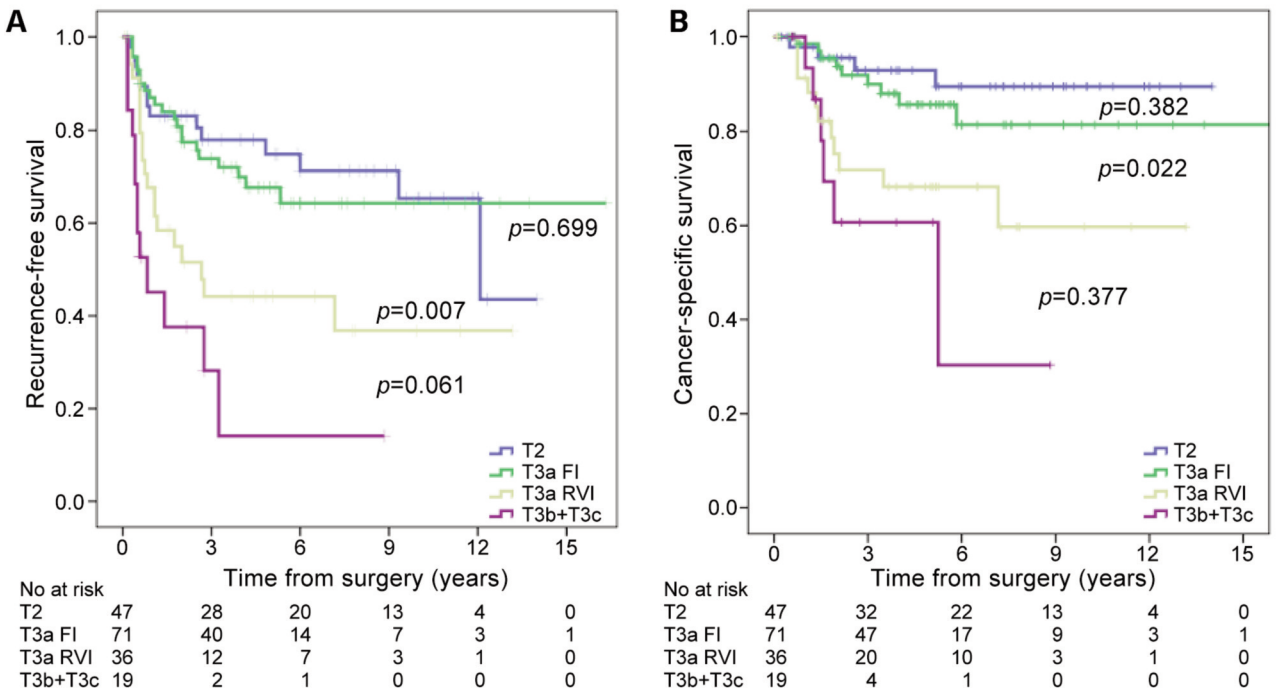

Figure 1. *Recurrence free survival (A) and cancer specific survival (B) among the 4 groups: T2, T3a with fat invasion (FI), T3a with renal vein invasion (RVI) and T3b+T3c.*

Patients with renal tumors having both renal vein invasion and fat invasion had similar RFS and CSS when compared to those with renal vein invasion only (Figure 2). When taking tumor size into consideration, we found that renal tumors greater than 7 cm with fat invasion showed poor oncologic outcomes in terms of RFS and CSS than their T2 counterparts (Figure 3).

Evaluation of predictive factors for RFS and CSS using the Cox proportional hazard model is delineated in Table II. Based upon univariable analysis, the T3a with RVI and T3b+T3c group were associated with a higher risk of tumor recurrence [T3a with RVI: Hazard ratio (HR)=2.28, 95% Confidence interval (95% CI)=1.22-4.27, p=0.01; T3b+T3c : HR=4.65, 95% CI=2.26-9.52, p<0.01] and disease related death (T3a with RVI: HR=2.67, 95% CI=1.11-6.46, p=0.029; T3b+T3c: HR=5.10, 95% CI=1.76-14.65, p=0.002). Based upon multivariable analysis adjusted for grade, size, necrosis and sacromatoid features, the T3a with RVI and T3b+T3c groups were associated with both worse RFS (T3a with RVI: HR=2.06, 95% CI=1.1-3.87, p=0.024; T3b+T3c: HR=3.6, 95% CI=1.74-7.45, p<0.001) and CSS (T3a with RVI: HR=2.46, 95% CI=1.01-6.0, p=0.048; T3b+T3c: HR=4.4, 95% CI=1.41-13.72, p=0.011), when compared to the T3a with FI group.

Discussion

In the present study, we analyzed the oncological outcomes of pT3a RCC according to various sites of extrarenal invasion and found that patients with RVI experienced an increased rate of tumor recurrence and cancer related death when compared to those with FI. Based upon the multivariable analysis, RVI was a predictive factor for tumor recurrence and survival.

According to the 8th AJCC TNM staging system (1), stage T3a RCC comprised various patterns of extrarenal extension, including SFI, PFI, PSI and RVI, amongst which patients should theoretically show similar prognosis. However, previously published literature has reported that the oncological outcomes of these pT3a RCC patients were heterogeneous, and the impact of different sites of extrarenal invasion was a subject of debate. RVI-only and FI-only tumors carried similar prognosis according to previous studies by Baccos *el al*. (9) and Shah *et al*. (10). Novara and his colleagues (11) reported that better prognosis was observed in the RVI group than the FI group. On the contrary, Part *et al*. (8) and Jung *et al*. (12) found that patients with RVI experienced poor survival rate and higher rate of disease recurrence. Our study also found that patients with RVI demonstrated poorer prognosis than did the FI

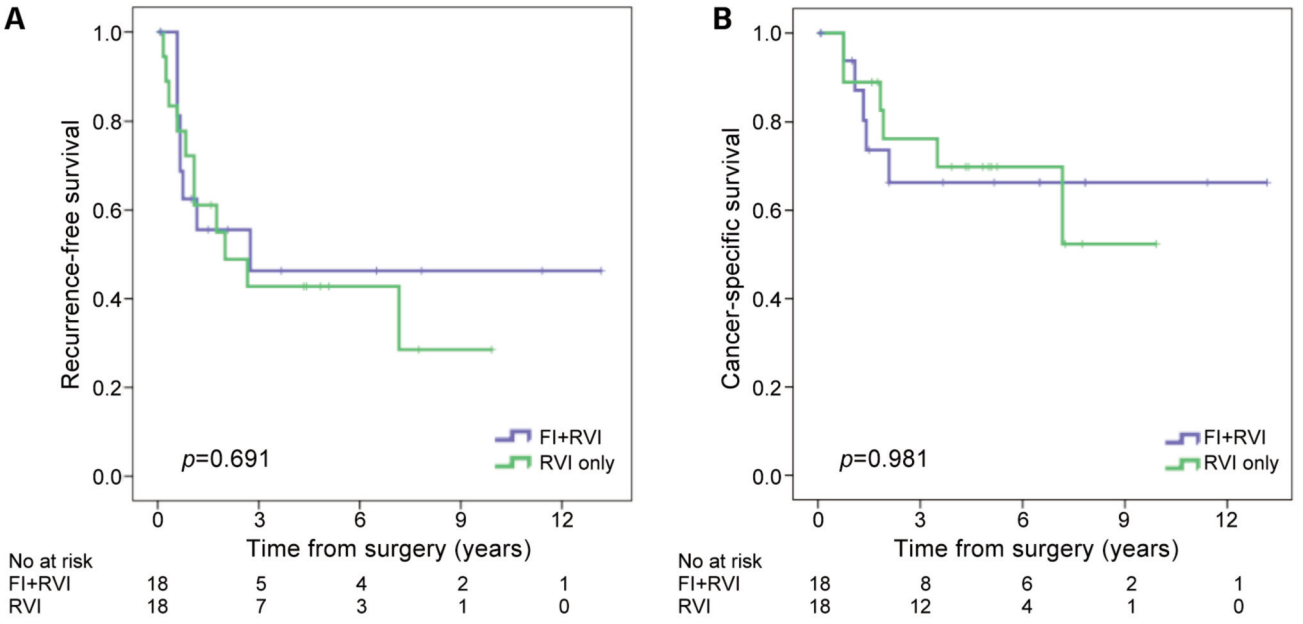

Figure 2. *Comparison of recurrence-free survival (A) and cancer specific survival (B) between renal vein invasion (RVI) only and RVI+fat invasion (FI) groups.*

group. The conflicting results which occurred among these studies may be attributed to the differences in tumor size, pathologic examination and small sample sizes.

The impact of SFI and PFI on prognosis, according to previous studies has been controversial (2-6). Poon *et al*. observed that both the SFI and PFI have a comparable influence on oncologic outcomes (7). The present study also found that there was no significant difference in survival and tumor recurrence between those patients with SFI and PFI. Thus, both of the parameters were combined into the FI group in the present study.

Shah *et al*. (10) reported that isolated SFI, PFI or RVI carry similar prognostic impacts and the presence of multiple patterns of extrarenal invasion was associated with a higher risk of disease recurrence and cancer related death. However, the present study found that patients with combined FI+RVI are given a similar prognosis as the patients with RVI-only tumors (Figure 2). This may be attributed to that the more aggressive nature of RVI and it overweighed the influence of FI on prognosis. Therefore, patients with FI+RVI were categorized and placed in the RVI group in our study.

Conventional RVI was considered for primary tumors with gross extension to the renal vein or its segmental branches. However, an analysis conducted by Part *et al*. (8) revealed that microscopic renal vein wall invasion was a prognostic factor for disease recurrence and cancer related death. In the series by Zini *et al*. (13) and Faba *et al*. (14) also reported that microscopic renal vein wall invasion was an independent prognostic indicator of inferior oncologic outcomes. Microscopic renal vein wall invasion is analogous to renal tumors with vena cava wall invasion, which is included in stage T3c in the 8th AJCC staging system (1), and demonstrates adverse pathologic features. Our study revealed that patients with T3b and T3c renal tumors experienced inferior RFS and CSS, although neither reached statistical significance, when compared to the T3a with RVI group. The discrepancy of these results can be explained by that the fact that the RVI group in the present study included patients with either renal vein thrombus or microscopic renal vein wall invasion.

The prognostic importance regarding tumor size and FI is controversial and many studies have investigated the differences between these factors. Previous literature has reported that patients with pT3a RCC <4 cm experienced similar outcomes when compared to those with pT1a RCC (15, 16). Studies performed by Gilbert *et al*. (17) suggested that the patients with pT3a and pT1-2 RCC experienced comparable 5-year RFS rates. However, several studies have demonstrated a worse prognosis in patients with pT3a RCC upstaging from clinical stage T1a renal tumors (18, 19). In the present study, we found that RFS and CSS of patients with FI renal tumors were not different from that of pT2. This may result from tumor size having an impact on prognosis for FI patients, and our cohort included patients with renal tumor size smaller and larger than 7 cm. In fact, a subgroup analysis in the present study revealed that patients with FI RCC >7 cm had significantly inferior 5-year RFS and CSS than patients in the pT2 group (RFS: FI *vs*. T2 42.1% *vs*. 76.8%, p=0.02; CSS: FI *vs*. T2 70.1% *vs*. 95.4%,

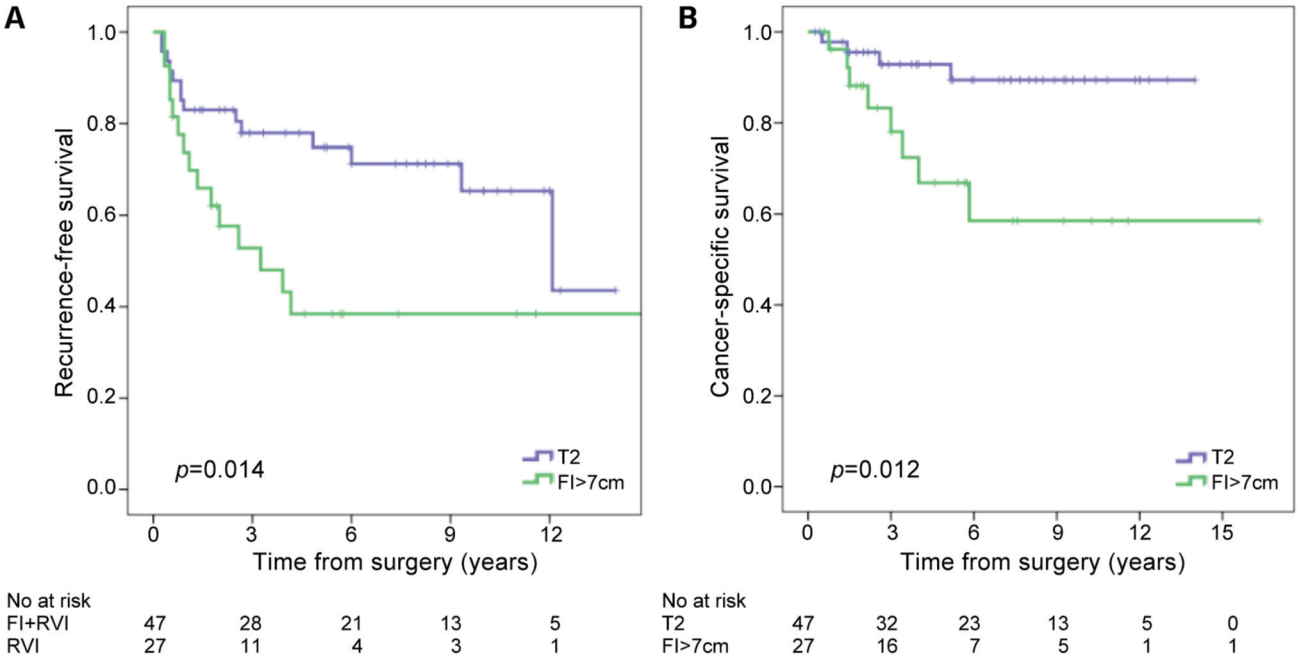

Figure 3. *Comparison of recurrence-free survival (A) and cancer-specific survival (B) between T2 and T3a with fat invasion (FI) greater than 7 cm groups.*

p=0.001). These results were compatible with the researches performed by Jeon *et al*. (20) and Yoo *et al*. (21), which showed that FI was an independent prognostic factor for RFS and CSS in pT3a tumors larger than 7 cm.

Precise tumor staging and risk stratification are cornerstones for evaluating patients' prognosis and deciding postoperative follow-up protocol. With increased interest in neoadjuvant and adjuvant systemic therapy for RCC in recent years, it is important to stratify patients accurately (22-24). In addition to the influence of different extrarenal extension sites on oncologic outcomes (2-9), Jang *et al*. reported that high minichromosome maintenance (MCM) gene expression level was a predictor of tumor progression and metastasis (25). In the present study, we showed that patients with RVI experienced inferior outcomes compared to those with FI, and that most of disease recurrence involved distant metastasis. This further emphasized the role of adjuvant systemic therapy for advanced RCC, as well as accurate patient classification.

Several limitations exist in the present study. The retrospective data collection and limited sample sizes were subject to inherent biases. The present study included various histological subtypes of RCC and different surgical approaches, which may influence the accuracy when evaluating results. Furthermore, the data of this research spanned from 2000 to 2018, and a lack re-review of the pathological specimens by a urological pathologist also resulted in biases.

Table II. *Cox proportional hazard regression models for prognosis.*

	Univariable recurrence HR (95% CI)	*p*-Value	Multivariable recurrence HR (95% CI)	*p*-Value
T2	0.88 (0.44-1.28)	0.7	0.68 (0.33-1.38)	0.285
T3a FI	Reference		Reference	
T3a RVI	2.28 (1.22-4.27)	0.01*	2.06 (1.10-3.87)	0.024*
T3b+T3c	4.65 (2.26-9.52)	<0.001*	3.60 (1.74-7.45)	<0.001*
	Univariable CSS HR (95% CI)		Multivariable CSS HR (95% CI)	
T2	0.59 (0.18-1.94)	0.387	0.52 (0.16-1.71)	0.279
T3a FI	Reference		Reference	
T3a RVI	2.67 (1.11-6.46)	0.029*	2.46 (1.01-6.0)	0.048*
T3b+T3c	5.10 (1.76-14.65)	0.002*	4.40 (1.41-13.72)	0.011*

CI: Confidence interval; CSS: cancer specific survival; FI: fat invasion; HR: hazard ratio; RVI: renal vein invasion. *Statistically significant *p*-values. Adjusted for grade, size, necrosis and sacromatoid features.

In conclusion, the present study reveals that patients with RCC extending to renal veins experience worse RFS and CSS than patients with RCC invading to sinus fat or perinephretic fat. RCC with combined RVI and FI did not show inferior prognosis compared to those with isolated RVI. Tumor size should be taken into consideration when evaluating the prognostic impact of pT3a RCC. These findings assist in the

stratification of patients with pT3a RCC when providing a prognosis and deciding upon follow-up protocol, as well as implementing the use of adjuvant therapy.

Conflicts of Interest

There are no conflicts of interest.

Authors' Contributions

The study was designed by GSL and JRL. Data were provided and analyzed by JRL, SSW, CSC, CKY, SCH, CLC, YCO and KYC. The article was drafted by GSL. All Authors have read and approved the manuscript for publication.

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