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Clinical-Kidney cancer

The prognostic value of the site of invasion in T3aN0M0 clear cell renal cell carcinoma

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Abstract

Background: The 7th Tumor-Node-Metastasis system for clear cell renal cell carcinoma (ccRCC) classified renal sinus fat invasion (SFI), perirenal fat invasion (PFI), or renal vein invasion (RVI) as stage pT3a. However, their close interactions and prognostic value of them remain controversial. The goal of this study is to further analyze their prognostic values for patients with T3aN0M0 ccRCC.

Methods: The data of 1,869 pT3aN0M0 ccRCC patients receiving the radical nephrectomy surgery were collected from the National Cancer Institute Surveillance, Epidemiology, and End Results database of United states from 2010 to 2014. These Patients were grouped as SFI, PFI, SFI + RVI, SFI + PFI, PFI + RVI, and SFI + PFI + RVI according to their corresponding manifestations. Cancer-specific survival (CSS) was determined using the Kaplan−Meier method. Univariate and Multivariate cox proportional-hazards regression methods were used to evaluate the impacts of clinical pathologic parameters on CSS.

Results: Patients with SFI or PFI alone had the similar CSS ($P = 0.286$) and patients with SFI + PFI + RVI had the worst outcomes. Moreover, significantly more patients with SFI + PFI + RVI had tumor diameter ≥7 cm than patients with PFI + RVI, SFI + PFI (68.80% vs. 65.32%, 58.77%, and 55.04%, $P = 0.026$), respectively. Multivariable analysis showed that RVI + PFI ($P = 0.013$) and PFI + SFI + RVI ($P = 0.011$) were the independent factors of CSS.

Conclusions: The results suggest that invasion location can help distinguish patients with T3aN0M0 ccRCC with increased risk of cancer-related mortality.

Keywords: Renal sinus fat invasion; Perirenal fat invasion; Renal vein invasion; Renal cell carcinoma; Cancer-specific survival

1. Introduction

The most recently 7th Tumor-Node-Metastasis (TNM) classification system defined the renal sinus fat invasion (SFI), perinephric fat invasion (PFI), and renal vein invasion (RVI) as T3a stage of renal cell carcinoma (RCC) [1]. In this edition, the RVI was down-staged from T3b to T3a, and adrenal invasion was up-staged from T3a to T4 [1]. T3a is the major component of T3 stage. According to the 7th edition, T3a patients account for 88.1% of the whole T3 patients, while only account for about 45% in the 6th edition [2].

The 3 factors (SFI, PFI, and RVI) were supposed to be equal for the prognosis of T3a patients. However, their prognostic values are controversial in the previous reports. Bedke et al. showed that SFI was a better prognostic factor than PFI [3], while Zhang et al. found that T3a RCC patients with SFI had significantly poorer cancer-special survival (CSS) ($P < 0.001$) than those with PFI [4] and

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Poon et al. reported that the prognosis of patients with SFI and patients with PFI seems to be comparable [5]. Park et al. found that the impacts of PFI and RVI, but not others on CSS were similar [6]. Meanwhile, some researchers demonstrated that RCC patients presenting concomitant invasion of the RVI and PFI have significantly worse survival rates than those showing any of the parameters separately [7]. Therefore, the previous reports on the different prognostic value of SFI, PFI, and RVI for T3a RCC are controversial and the prognostic value of combinations of these 3 factors on CSS is not well explored.

Although the 7th edition of the American Joint Committee on Cancer RCC staging system stages these 3 risk factors into T3a stage, further refined prognostic information should be evaluated. We sought to determine the relationship between the clinicopathologic characteristics of ccRCC patients and the 3 factors in a large dataset of 1,869 surgically treated T3aN0M0 ccRCC patients and identified their different prognostic values.

2. Materials and methods

2.1. Patient source

National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database collects data derived from 17 cancer registries, which stands for 28% of the United States' population. A total of 230, 634 renal parenchyma tumor cases (C64.9) were reported to SEER database from 1979 to 2014. A total of 1,869 patients with clinical features corresponding to the histology codes 8310/3 (clear cell adenocarcinoma), surgery codes 40 or 50 (radical nephrectomy), and pT3aN0M0 site code (the 7th TNM edition) of the international classification of disease for oncology (ICD-O-3) between 2010 and 2014 and diagnosed with risk factors of SFI, PFI, and RVI using the CS extension and CS Site-Specific Factor 1 code were ultimately included to our investigation. The event of CSS was provided by SEER cause-specific death classification coding system. Tumor diameter, and sarcomatoid features were characterized according to the CS tumor size and CS Site-Specific Factor 4, respectively. In addition, all the cases were extracted from the SEER database using the SEER Stat 8.3.5 software (National Institutes of Health, Bethesda, MD). The SEER database includes deidentified patients' information. This research was exempt from approval.

2.2. Statistical analyses

Continuous variables were reported as the mean ± standard deviation. The Kruskal−Wallis test was used to compare the means of continuous variables and the chi-square test was used to compare the categorical variables. CSS curves were estimated using the Kaplan−Meier method and compared using the log-rank test. Survival analysis was performed using univariable and multivariate Cox proportional hazards methods. All data were evaluated using SPSS version 24.0 (SPSS Inc., Chicago, IL) and all reported P values were 2-sided with statistical significance set at $P < 0.05$.

3. Results

A total of 1,869 T3aN0M0 ccRCC patients submitted to radical nephrectomy from 2010 and 2014 in SEER database were included in the study. They were 64.72 ± 11.25 years old in average. Among them, 1,318 (70.52%) were males, 4.92% had sarcomatoid differentiation, 51.63% had tumors with diameter > 7 cm and 58.48% had tumors at grade of 3−4. Of 1,869 patients, 381 patients had SFI only, 687 had PFI only, 337 had SFI + RVI, 105 had SFI + PFI, 234 had PFI + RVI, and 125 had SFI + PFI + RVI. Due to the lack of information in the SEER database, there are no data available for patients with RVI only in this cohort. Among these 6 groups, the rate of patients with tumor diameter ≥7 cm was 44.09%, 45.56%, 55.49%, 57.14%, 65.53%, and 68.80%, respectively ($P < 0.001$), the rate of patients with sarcomatoid differentiation was 3.41%, 2.91%, 5.64%, 7.62%, 8.55%, and 9.60%, respectively ($P < 0.001$), and the rate of patients with grade 3−4 was 57.22%, 52.40%, 64.39%,53.33%, 67.09%, and 68.00%, respectively ($P < 0.001$). Table 1 lists the information of all patients and the characteristics of the tumors.

The mean CSS for T3aN0M0 ccRCC patients of SFI, PFI, SFI + RVI, SFI + PFI, PFI + RVI, and SFI + PFI + RVI was 55.69, 54.07, 53.82, 52.32, 50.33, and 48.30 months, respectively. Based on our Kaplan−Meier survival curves for CSS, there was no significant difference in CSS between patients with SFI only and patients with PFI only ($P = 0.286$) (Fig. 1A). Patients with PFI + RVI had the worst CSS and there was a significant difference in CSS between patients with SFI + RVI and patients with PFI + RVI ($P = 0.012$) (Fig. 1B, Table 2), but not between patients with PFI + RVI and patients with SFI + PFI ($P = 0.402$). Overall, patients with SFI + PFI + RVI had the worst CSS among all the patients, showing significant difference from patients with SFI ($P < 0.001$), patients with PFI ($P < 0.001$), and patient with SFI + RVI ($P = 0.003$), but not from patients with SFI + PFI ($P = 0.172$) and patients with PFI + RVI ($P = 0.477$). (Fig. 1B, Table 2).

Among all the patients, univariable analysis demonstrated that RVI + PFI and PFI + SFI + RVI were predictor of poor CSS ($P < 0.001$ for both). In addition, grade ($P < 0.001$), tumor diameter ($P < 0.001$), and sarcomatoid differentiation ($P < 0.001$) were also significant predictors of CSS. Multivariate Cox proportional hazards method showed that RVI + PFI ($P = 0.013$), PFI + SFI + RVI ($P = 0.011$), tumor grade ($P < 0.001$), tumor diameter ($P < 0.001$) and sarcomatoid differentiation ($P < 0.001$) were also significant predictors of CSS (Table 3).

The patients were further sub-grouped according to individual factor (SFI or PFI only) and combinational factors (RVI + SFI, SFI + PFI, PFI + RVI, or PFI + SFI + RVI). In

Table 1
Clinicopathological characteristics of the 1,869 patients with T3aN0M0

Variables	Total (n = 1869)	SFI (n = 381)	PFI (n = 687)	RVI + SFI (n = 337)	SFI + PFI (n = 105)	PFI + RVI (n = 234)	PFI + SFI + RVI (n = 125)	P value
Age at diagnosis (Mean + SD)	64.72 ± 11.25	62.93 ± 10.96	65.32 ± 11.38	64.42 ± 11.28	64.3 ± 12.08	65.52 ± 11.15	66.58 ± 10.33	0.010
Gender								0.422
Male	1318 (70.52%)	259 (67.98%)	481 (70.01%)	243 (72.11%)	80 (76.19%)	161 (68.80%)	94(75.20%)	
Female	551 (29.48%)	122 (32.02%)	206 (29.99%)	94 (27.89%)	25 (23.81%)	73 (31.20%)	31 (24.80%)	
Grade								<0.001
Grade I + Grade II	776 (41.52%)	163 (42.78%)	327 (47.60%)	120 (35.61%)	49 (46.67%)	77 (32.91%)	40 (32.00%)	
Grade III + Grade IV	1093 (58.48%)	218 (57.22%)	360 (52.40%)	217 (64.39%)	56 (53.33%)	157 (67.09%)	85 (68.00%)	
Tumor Diameter								<0.001
<7 cm	904 (48.37%)	213 (55.91%)	374 (54.44%)	150 (44.51%)	45 (42.86%)	83 (35.47%)	39 (31.20%)	
≥7 cm	965 (51.63%)	168 (44.09%)	313 (45.56%)	187 (55.49%)	60 (57.14%)	151 (64.53%)	86 (68.80%)	
Sarcomatoid differentiation								<0.001
No	1777 (95.08%)	368 (96.59%)	667 (97.09%)	318 (94.36%)	97 (92.38%)	214 (91.45%)	113 (90.40%)	
Yes	92 (4.92%)	13 (3.41%)	20 (2.91%)	19 (5.64%)	8 (7.62%)	20 (8.55%)	12 (9.60%)	

Abbreviations: SFI = sinus fat invasion; PFI = perinephric fat; RVI = renal vein invasion.

individual factor (SFI or PFI only) group, the tumor diameter (P = 0.645), sarcomataiod differentiation (P = 0.650), and tumor grade (P = 0.130) were not significantly different between patients with SFI only and patients with PFI only. However, in the combinational factor (RVI + SFI, SFI + PFI, PFI + RVI or PFI + SFI + RVI) group, the rate of patients with tumor diameter ≥7 cm was 68.80% for patients with PFI + SFI + RVI, 55.49% for patients with SFI + RVI, 57.14% for patients with SFI + PFI, and 64.53% for patients with PFI +RVI, showing statistically significant difference (P = 0.026). But the rates of patients with sarcomataiod differentiation (P = 0.411) and tumor grade 3−4 (P = 0.071) were not significantly different among patients with PFI + SFI + RVI, SFI + RVI, SFI + PFI or PFI + RVI (Supplementary Table 1).

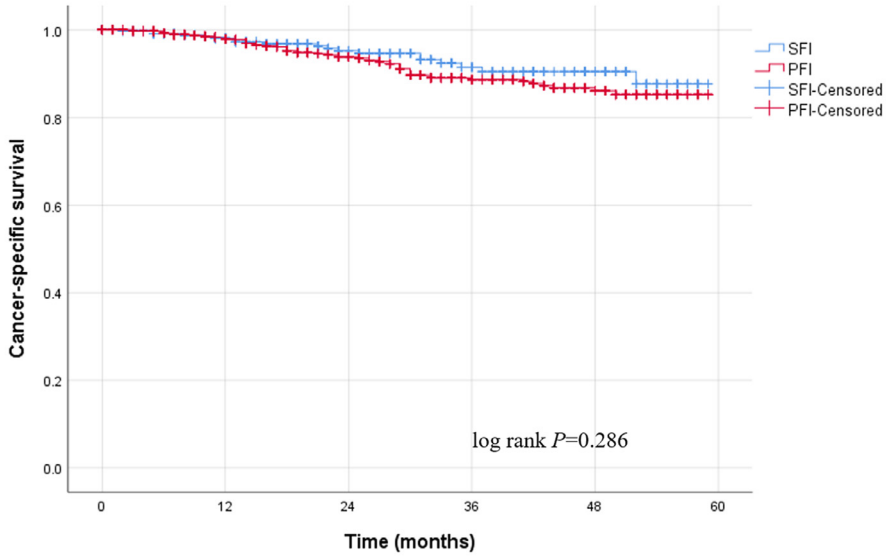
4. Discussion

In the present study, we analyzed the different prognosis of pT3aN0M0 ccRCC patients with SFI only, PFI only or in combination in a large cohort based on SEER database. The results showed that patients with SFI only had similar CSS to patients with PFI only. In addition, patients with SFI + PFI + RVI had the lowest CSS compared to patients with RVI + SFI/PFI + RVI/SFI + PFI. Moreover, SFI + PFI + RVI and PFI + RVI were independent factors of CSS, but not SFI + RVI and SFI + PFI. There were significantly more patients with PFI + SFI + RVI who had tumor diameter ≥7cm than patients with SFI+RVI/SFI +PFI/PFI+RVI (P = 0.026), but the number of patients with PFI + SFI + RVI who also had sarcomatoid differentiation (P = 0.411) or tumor grade 3−4 (P = 0.071) was not significantly different from that of patients with SFI + RVI/SFI + PFI/PFI + RVI.

In addition, we only included T3aN0M0 ccRCC patients to exclude the effect of nonclear cell RCC subtypes, lymph node, and distant metastasis. The results showed that patients with SFI (n = 381) and patients with PFI (n = 687) had median CSS of 55.69 months and 54.07 months, respectively, showing no significant difference (P = 0.275). These 2 types of patients also had similar rate of patients with tumor diameter ≥7 cm (44.09% vs. 45.56%), sarcomatoid change (3.41% vs. 2.91%), and tumor grade of 3−4 (57.22% vs. 52.40%). Kresowik et al. showed that there was no difference in CSS between patients with SFI and patients with PFI (P = 0.248) [8]. Margulis et al. also showed no significant difference in 5-year CSS between patients with SFI (n = 166), and patients with PFI (n = 199) (50.8% vs. 54.1%, P = 0.782) [9]. Moreover, no significant differences in CSS and disease-free survival were seen between patients with SFI and patients with PFI at partial nephrectomy of T3a stage [10]. Our study also showed that SFI only and PFI only had similarly prognostic value for patients at T3a stage.

Overall, it seems inherent that patients with PFI + SFI + RVI have more aggressive biology and this seems to be supported by data in Table 1 showing larger size,

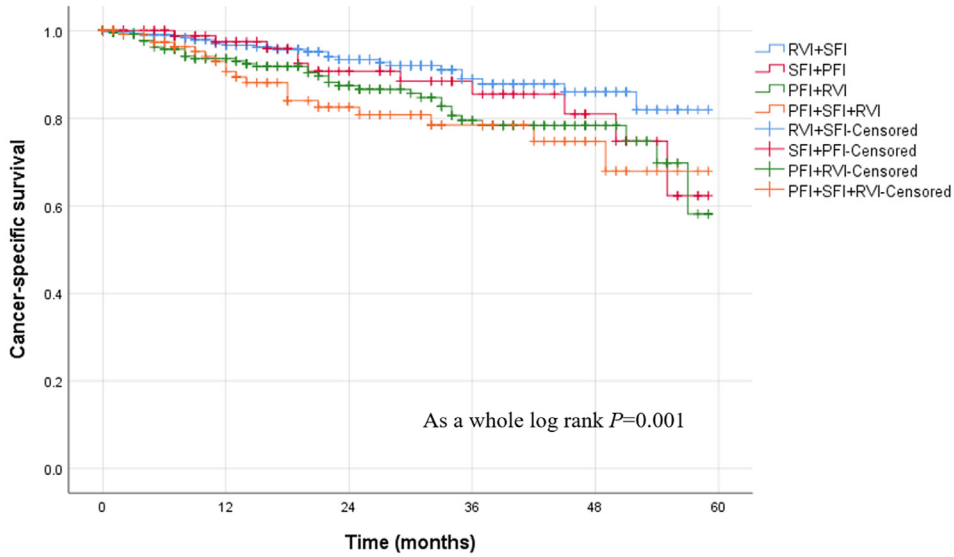
A



Number at risk

SFI	381	254	167	97	48	0
PFI	687	511	381	245	125	0

B



Number at risk

RVI+SFI	337	229	149	78	40	0
SFI+PFI	105	70	45	30	13	0
PFI+RVI	234	162	113	69	32	0
PFI+SFI+RVI	125	78	50	28	12	0

Fig. 1. Cancer-specific survival of T3aN0M0 ccRCC based on the invasion site. (A) Patients with SFI or PFI alone. (B) Patients with 2 or 3 combined invasions (RVI + SFI, SFI + PFI, PFI + RVI or PFI + SFI + RVI).

Table 2
Pairwise comparisons among different groups by log rank test

		SFI		PFI		RVI + SFI		SFI + PFI		PFI + RVI		PFI + SFI + RVI	
		Chi-square	*P* value	Chi-square	*P* value	Chi-square	*P* value	Chi-square	*P* value	Chi-square	*P* value	Chi-square	*P* value
Log rank (Mantel-Cox)	SFI	–	–	1.140	0.286	1.150	0.284	3.689	0.055	13.474	**<0.001**	15.608	**<0.001**
	PFI	1.140	0.286	–	–	0.016	0.900	1.804	0.179	11.172	**0.001**	12.454	**<0.001**
	RVI+SFI	1.150	0.284	0.016	0.900	–	–	1.038	0.308	6.290	**0.012**	8.693	**0.003**
	SFI+PFI	3.689	0.055	1.804	0.179	1.038	0.308	–	–	0.702	0.402	1.869	0.172
	PFI+RVI	13.474	**<0.001**	11.172	**0.001**	6.290	**0.012**	0.702	0.402	–	–	0.505	0.477
	PFI + SFI + RVI	15.608	**<0.001**	12.454	**<0.001**	8.693	**0.003**	1.869	0.172	0.505	0.477	–	–

Abbreviations: SFI = sinus fat invasion; PFI = perinephric fat; RVI = renal vein invasion.

higher grade, and more sarcomatous differentiation in those patients. However, because T3a RCC patient may have more than 1 manifestation, we further analyzed the prognostic values of SFI + PFI, SFI + RVI, RVI + PFI, RVI + SFI + PFI for T3aN0M0 ccRCC patients. The results showed that patients with SFI + RVI + PFI had the worst CSS of 48.30 months in average, followed in turn by that of 50.33 months of patients with PFI + RVI, 52.32 months of patients with RVI + SFI and 53.82 months of patients with SFI + PFI. Moreover, patients with SFI + RVI + PFI had significantly higher rate of tumor diameter ≥7 cm compared with that of patients with SFI + PFI, RVI + SFI or PFI + RVI (68.80% vs. 64.53%, 57.14%, and 55.49%, $P = 0.026$), but not in sarcomatoid differentiation (9.60% vs. 8.55%, 7.62%, and 5.64%, $P = 0.411$) and tumor grade 3−4 (68.00% vs. 67.09%, 53.33%, and 64.39%, $P = 0.071$). Moreover, univariate and multivariate analyses showed that SFI + RVI + PFI and PFI + RVI, but not SFI + PFI and RVI + SFI, were independent prognostic factors of poor CSS in T3aN0M0 ccRCC patients.

Few studies had directly compared the prognostic value of combination of different factors for T3aN0M0 ccRCC patients. Recently, Park et al. [6] reported that compared with patients with PFI + SFI, patients with RVI + perinephric invasion (PNI) ± SFI had lower 5-years RFS (30.0% vs. 46.9%) and CSS (61.4% vs. 69.1%), higher percentages of patients with higher tumor grade (34.8% vs. 24.1%) and sarcomatoid change (11.3% vs 6.9%). However, the study had a relatively small sample size and included patients with no-clear cell subtypes. Moreover, they used a mixed factor of RVI + PNI with or without SFI and did not include RVI + SFI and RVI + PNI

Table 3
Univariable and multivariate analyses of prognostic factors for cancer-special mortality in T3aN0M0 patients with ccRCC

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age at diagnosis	1.01 (1.00, 1.03)	0.064		
Gender				
Male	1.00 (ref.)			
Female	1.04 (0.74, 1.45)	0.827		
Grade				
Grade I + Grade II	1.00 (ref.)		1.00 (ref.)	
Grade III + Grade IV	3.17 (2.16, 4.64)	<0.001	2.23 (1.50, 3.32)	<0.001
Tumor Diameter				
<7 cm	1.00 (ref.)		1.00 (ref.)	
≥7 cm	2.69 (1.91, 3.79)	<0.001	2.08 (1.46, 2.95)	<0.001
Sarcomatoid differentiation				
No	1.00 (ref.)		1.00 (ref.)	
Yes	7.89 (5.22, 11.93)	<0.001	5.07 (3.29, 7.81)	<0.001
Group				
SFI	1.00 (ref.)		1.00 (ref.)	
PFI	1.34 (0.79, 2.25)	0.275	1.34 (0.79, 2.26)	0.268
RVI + SFI	1.39 (0.75, 2.55)	0.292	1.22 (0.66, 2.24)	0.523
SFI + PFI	2.06 (0.98, 4.33)	0.056	1.51 (0.71, 3.20)	0.279
RVI + PFI	2.73 (1.56, 4.78)	<0.001	2.05 (1.16, 3.62)	0.013
PFI + SFI + RVI	3.37 (1.78, 6.36)	<0.001	2.30 (1.21, 4.38)	0.011

alone group. Margulis et al. found that patients with SFI + PFI had similar CSS with patients with SFI or PFI only (5-year CSS: 50 ± 10%, 53 ± 4%, 49 ± 8%, $P = 0.543$) [9], while other researchers reported that patients with SFI + PFI had worse CSS than patients with SFI or PFI alone [8]. Our results showed that SFI + PFI, RVI + SFI, PFI + RVI or SFI + PFI + RVI had different prognostic values for CSS. Patients with SFI + PFI + RVI had worse CSS than patients with SFI + PFI, RVI + SFI or PFI + RVI, possibly because that the former had a significantly higher percentage of tumor diameter ≥7 cm ($P = 0.026$). Besides that, tumor diameter should be also considered as a risk factor of CSS at T3a stage.

Several groups have evaluated the role of tumor diameter in T3a RCC. Lam et al. found that patients with T3a RCC with diameter ≥7 cm had significantly worse CSS than patients with T2 stage RCC, while CSS of patients with combined T3a RCC and tumor diameter ≤7 cm did not differ from that of patients with T2, combined T3a and tumor diameter ≥7 cm, and T3b [11]. Similarly, Yoo et al. concluded that tumor diameter was the strongest prognostic factor of CSS and should be included in T3a stage [12]. However, the above-mentioned studies were based on the 6th edition of the TNM classification for T3a RCC study. Recently, based on the 7th edition of the TNM classification, Zhang et al. reported that T3aN0M0 RCC patients with tumor diameter ≥7 cm had shorter estimated 5-year CSS (46.6% vs. 75.0%, $P = 0.003$) and RFS (35.6% vs. 62.7%, $P = 0.011$) compared with those with tumor diameter ≤7 cm. Among them, those with higher rate of symptoms during diagnosis, higher Fuhrman grades, and more necrosis features were more likely to invade the collecting system and renal vein [13]. Brookman-May et al. also showed that tumor diameter could significantly influence cancer-specific mortality: tumor diameter increasing 1 cm was associated with a 7% increase in CSM and a cutoff of 7 cm was the optimal and practical means to stratify the significantly different prognoses among pT3a RCC patients [14]. Our results also revealed that tumor diameter ≥ 7 cm was associated with the worse CSS of pT3aN0M0 ccRCC patients, consistent with aforementioned studies.

Although our research is the large study of different prognostics of the combination of SFI, PFI, and RVI in T3aN0M0 ccRCC patients, it has several limitations. First, it is a retrospective study and lack of standardization for diagnostic procedures, therapy, and follow-up. Second, some information is not available such as smoking status, laboratory test results, metastatic patterns, adjuvant therapy, and treatment after recurrence. Third, no central pathology review was performed to reconfirm the pathologic parameters as SFI, PFI, and RVI. Fourth, patients with RVI alone are not described in the current database, therefore the prognostic of RVI was not assessed for the entire study cohort. Fifth, the follow-up time is not long enough because the data were collected since 2010, just after the release of the 7th edition of TNM system. Although the American Joint Committee on Cancer introduced several changes into the 8th edition staging system of RCC [15], the SEER database has not been updated yet. Future studies should collect the data containing SFI, PFI or RVI alone from multi-centers to valid the prognostic value of the 3 factors.

5. Conclusions

T3N0M0 ccRCC patients with SFI only had the similar CSS to those with PFI only, and ccRCC patients with SFI + PFI + RVI had lower CSS than those with SFI + PFI, SFI + RVI or PFI + RVI. SFI + PFI + RVI and PFI + RVI were 2 independent prognostic factors for poor CSS of T3aN0M0 ccRCC patients besides the tumor diameter ≥7 cm and sarcomatoid differentiation, and tumor diameter ≥7 cm is associated with worse CSS compared with RVI + PFI, RVI + SFI, and SFI + PFI. Hence, besides SFI and PFI alone in patients, tumor diameter should also be considered as a factor affecting the decision-making for follow-up and treatment strategy of patients after surgery.

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Conflict of Interest Disclosures

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.01.019.

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