Significance of Tumor Size in Renal Cell Cancer with Perinephric Fat Infiltration

Is TNM Staging System Adequate for Predicting Prognosis?

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Purpose: To evaluate the influence of perinephric fat infiltration and tumor size on survival of patients with renal cell carcinoma (RCC).

Materials and Methods: We have retrospectively reviewed the records of 338 consecutive patients with pT1-3aN0M0 RCC, including 275 pT1-2 and 63 pT3a tumors, who underwent open partial or radical nephrectomy between 1995 and 2008. Univariate and multivariate analyses were performed in order to evaluate the prognostic factors.

Results: Median follow-up period was 36.07 months. Receiver Operating Characteristic curve analysis determined the optimal tumor size cutoff value as 7 cm (Area Under the Curve: 0.65 ± 0.047; 95% Confidence Interval: 0.558 to 0.741). Perinephric fat invasion and Fuhrman grade were independent prognostic factors for disease-specific survival (DSS). In patients with tumor size >7 cm, perinephric fat invasion affected DSS significantly. Tumor size (according to the cutoff value of 7 cm) significantly affected DSS in patients with pT3a disease. According to the TNM 2002 staging system, perinephric fat invasion did not have any significant effect on DSS in patients with tumor size smaller than 4 cm, unlike tumor size of 4 to 7 cm and >7 cm. pT3a tumors larger than 7 cm demonstrated the worst prognosis compared to other groups.

Conclusion: Perinephric fat invasion was demonstrated as a significant prognostic factor for RCC patients with tumor size >4 cm. Consequently, evaluation of pT3a patients should take tumor size into consideration for better prognostic analysis.

Keywords: renal cell carcinoma, prognosis, fatal outcome, humans

INTRODUCTION

Pathologic staging according to TNM staging system has been accepted as the most important prognostic predictor in patients with renal cell carcinoma (RCC).[1,2] Renal cell carcinoma was included initially in the TNM staging system in 1974.[3] Later on, several modifications have been generated to increase the prognostic accuracy of this staging system.

These modifications mostly concern the tumor size cutoff value. The 1987 TNM staging system used 2.5 cm as a cutoff value to differentiate pT1 and pT2 tumors.[4] This tumor size cutoff value was converted to 7 cm in the 1997 TNM staging system.[5] The 2002 TNM edition augmented the previous one by subdividing pT1 tumors according to a 4-cm cutoff value.[6] Distinctly, these revisions did not include pT3a tumors. However, using perinephric fat infiltration as a prognostic factor is still unclear.[7] Recent studies demonstrated different results and achieved contrary conclusions.[8,9]

The aim of this study is to evaluate the influence of perinephric fat infiltration and tumor size on patient's survival and to analyze whether tumor size should participate in staging patients with perinephric fat infiltration.

MATERIALS AND METHODS

A total of 488 patients with renal tumor diagnosis underwent open partial and radical nephrectomy at our clinic between 1995 and 2009. After excluding patients with histopathologically diagnosed benign tumors, patients who had inadequate follow-up, and patients who had pathologic stage higher than pT3a, 338 patients were diagnosed as pT1-3aN0M0 RCC and formed the basis of this study. Patients with pT3a RCC were not included in the study due to the adrenal invasion at diagnosis. Patients with lymph node or distant metastasis were excluded from the study as well.

Of 338 patients, 108 (32.0%) had pT1a, 98 (29.0%) had

pT1b, 69 (20.4%) had pT2, and 63 (18.6%) had pT3a tumors. The medical records of these patients were reviewed. All the patients were evaluated pre-operatively with abdominal computed tomography, abdominal ultrasonography, and chest x-ray. Subsequently, all tumor specimens were examined for tumor size, Fuhrman grade, and histological cell subtype. The 2002 TNM staging system was used for pathologic staging. Fuhrman grading system and Heidelberg histologic classification were employed to define the tumor grade and histologic subtype, respectively. The follow-up protocol included chest and abdominal imaging three times within the 1st year, twice in the 2nd year, and annually thereafter.

Student's *t* test and Pearson Chi-Square test were used to compare the means of continuous and categorical variables, respectively. Disease-specific survival (DSS) was defined as mortality due to RCC progression and estimated using the Kaplan Meier method. A Receiver Operating Characteristic (ROC) curve analysis was used to assign the optimal cutoff value for tumor size on DSS. Univariate analysis was employed to determine the relationship between prognostic factors and DSS. Multivariate analysis was performed by a Cox regression model with respect to potential influencing factors. Statistical significance in this study was defined as $P < .05$. All statistical analyses were performed by SPSS software (the Statistical Package for the Social Sciences, Version 13.0, SPSS Inc, Chicago, Illinois, USA).

RESULTS

The median postoperative follow-up period was 36.07 months (range, 1 to 145 months). Of 338 patients, 35 (10.3%) died because of RCC, including 18 (6.5%) in pT1-2 and 17 (26.9%) in pT3a staged patients ($P < .001$). Five-year DSS was 88.6% (± 2.8) for pT1-2 and 56.7% (± 5.1) for pT3a patients ($P < .001$). Receiver Operating Characteristic curve analysis determined the optimal tumor size cutoff value as 7

Table 1. Multivariate analysis for disease-specific survival in patients with pT1-3aN0M0 renal cell carcinoma.

Variable	Hazard Ratio	95% Confidence Interval	*P*
Age	1.578	0.776 to 3.208	.208
Perinephric fat invasion	3.521	1.700 to 7.294	.001
Grade (Grades 1 to 2 vs Grades 3 to 4)	5.239	2.418 to 11.353	< .001
Tumor size (≤7 cm vs >7 cm)	1.624	0.806 to 3.272	.175

Table 2. Clinicopathological parameters compared according to the 7 cm cutoff value, which was defined by the ROC curve analysis.[*]

	Tumor size ≤7 cm			Tumor size >7 cm		
	PFI (-)	PFI (+)	P	PFI (-)	PFI (+)	P
No	31	206		32	69	
Gender			.062			.18
Male	25 (80.6%)	131 (63.6%)		23 (71.9%)	40 (58%)	
Female	6 (19.4%)	75 (36.4%)		9 (28.1%)	29 (42%)	
Mean age (± SD)	60.5 (± 10.5)	55.6 (± 11.7)	.031	59 (± 10.9)	56.7 (± 10.11)	.302
No cell type (%)[£]						.121
Clear cell	22 (75.8%)	154 (77.7%)	.346	30 (93.7%)	50 (73.5%)	
Papillary	6 (20%)	31 (15.6%)		2 (6.3%)	13 (19.1%)	
Chromophobe	1 (4.2%)	13 (7.4%)		0 (0%)	5 (7.4%)	
No grade (%)						.001
1 to 2	20 (64.5%)	159 (77.2%)		9 (28.1%)	48 (69.6%)	
3 to 4	11 (35.5%)	47 (22.8%)	.126	23 (71.9%)	21 (30.4%)	
Mean tumor size (± SD), cm	4.48 (± 1.42)	4.34 (± 1.49)	.543	10.01(± 1.79)	10.71(± 2.86)	.47
Death by RCC	5 (16.1%)	11 (5.4%)	.043	12 (37.5%)	7 (10.1%)	.001

[*]ROC indicates receiver operating characteristic; PFI, perinephric fat invasion; SD, standard deviation; and RCC, renal cell carcinoma.
[£]Histologic subtypes besides clear cell. Papillary and chromophobe subtypes were omitted for statistical accuracy and 327 patients were included for the analysis.

cm (Area Under the Curve: 0.65 ± 0.047; 95% Confidence Interval: 0.558 to 0.741) with 66% sensitivity and 67% specificity.

In the univariate analysis, high tumor grade (Grades 3 to 4) ($P < .001$), tumor size >7 cm ($P < .002$), and perinephric fat invasion ($P < .005$) were detected as significant prognostic factors for DSS. Multivariate analysis, however, exhibited only tumor grade and perinephric fat invasion as prognostic factors. The 7 cm tumor size cutoff value was not detected as an independent prognostic factor in multivariate analysis (Table 1).

Perinephric fat invasion and higher tumor grade were found to be more frequent in patients with tumor size >7 cm compared with patients who had tumor size ≤7 cm. The histological subtype distribution was similar between patients with tumor size >7 cm and ≤7 cm.

Clinicopathological parameters were compared according to perinephric fat invasion using the 7 cm cutoff value (Table 2). Perinephric fat invasion, especially in patients with tumor size >7 cm, affected DSS significantly (Figure). Tumor size (according to the cutoff value of 7 cm) significantly affected DSS in patients with pT3a disease (Figure, B versus D; $P = .018$). On the other hand, pT2 versus pT3a ≤7 cm and pT2 versus pT1 stages showed similar DSS outcomes (C versus B and C versus A, respectively). In patients with tumor size ≤7 cm, perinephric fat invasion displayed worse outcomes than patients without perinephric fat invasion (Figure, A versus B; $P = .01$).

To evaluate the prognostic effects of perinephric fat invasion according to the 2002 TNM staging system, univariate and multivariate analyses which include perinephric fat invasion, tumor grade, and age were performed in patients with tumor size ≤4 cm , 4.1 to 7 cm, and >7 cm. In patients with tumor size ≤4 cm, univariate and multivariate analyses did not detect perinephric fat invasion as a prognostic factor. Unlikely, in patients with tumor size of 4 to 7 cm and >7 cm, univariate and multivariate analyses demonstrated perinephric fat invasion as a significant prognostic factor (Table 3).

Disease-specific survival for renal cell carcinoma >7 cm and ≤7 cm.
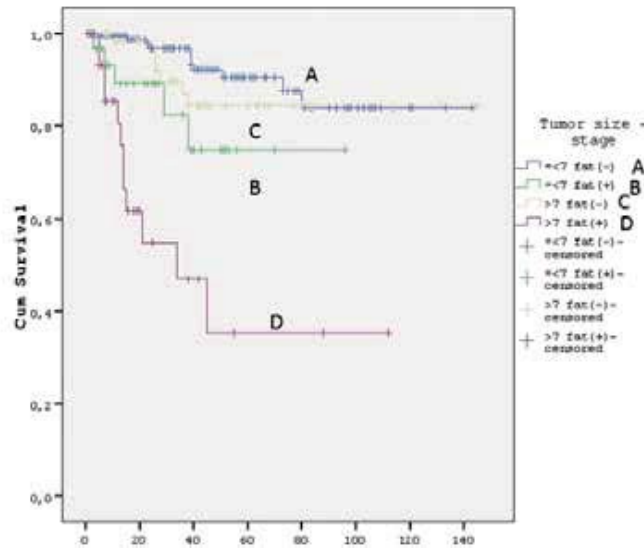
Table 3. Significance of perinephric fat invasion at multivariate analysis.

	Risk Ratio (95% Confidence Interval)	P
Tumors ≤4 cm		.618
No perinephric fat invasion	1.0	
Perinephric fat invasion	1.65 (0.22 to 12.04)	
Tumors 4 to 7 cm		.016
No perinephric fat invasion	1.0	
Perinephric fat invasion	8.3 (1.49 to 19.09)	
Tumors >7 cm		.001
No perinephric fat invasion	1.0	
Perinephric fat invasion	5.01 (1.85 to 13.52)	

DISCUSSION

Pathologic staging reflects the anatomical extent of the tumor and involvement of the adjacent tissues. Tumor size and perinephric fat invasion are basic features to classify the RCC according to the TNM staging system. Although evolution included many variables in the TNM staging system of RCC, tumor size was the leading one. Despite these revisions, recent studies offer new cutoff values for localized RCC patients.[10,11]

Unlike tumor size, perinephric fat invasion remained as a stable staging parameter regardless of tumor size. Perinephric fat invasion, without invasion to Gerota's fascia, is accepted as pT3a tumor regardless of tumor size in all recent TNM staging systems. However, the significance of perinephric fat invasion compared to tumor size is unclear.

Murphy and colleagues compared patients with pT2 and pT3a according to their clinicopathological features. The mean tumor size was 8.5 and 5.3 cm in patients with pT2 and pT3a renal tumors, respectively. The 5-year DSS was 68% for pT2 and 85% for pT3a patients. They pointed out that tumor size was more significant as a prognostic factor than perinephric fat invasion.[12] Siemer and associates, similar to our study, performed a ROC curve analysis to define the cutoff value for tumor size, according to the DSS. They have assigned 7 cm as a cutoff value. They have compared the outcomes of pT1, pT2, pT3a ≤7 cm, and pT3a >7 cm patients. The patients with pT1 and pT3a >7 cm RCC had the best and worst DSS rates, respectively. However, there were not any survival differences between patients with pT1 and pT3a ≤7 cm or pT2 and pT3a >7 cm. They had modified the staging of patients by merging all patients according to 7 cm cutoff value without considering perinephric fat invasion. Consequently, they demonstrated their modified T staging as a prognostic predictor, and proposed not to use perinephric fat invasion to assign T category.[7]

Siddiqui and coworkers divided the patients according to 2002 TNM staging system and evaluated the prognostic value of perinephric fat invasion. The univariate and multivariate analyses exhibited perinephric fat invasion as an unfavorable prognostic factor in all of the tumor size groups. They have concluded that utilizing tumor size for grouping pT3a is unnecessary.[8] Yoo and colleagues evaluated pT1-2 and pT3a patients in their recent study. They found out that patients with pT3a tumors >7 cm had significantly worse prognosis compared to patients with pT3a tumors ≤7 cm. The recurrence rate was 44.0% and 14.6%, respectively. The recurrence in pT3a >7 cm developed in multiple sites with large tumor burden. Their suggestion is to include tumor size for patients with perinephric fat invasion for higher staging efficiency.[9]

Aforementioned studies revealed that utilization of perinephric fat invasion in TNM staging system and classifying patients with perinephric fat invasion according to tumor size are unclear. To evaluate the prognostic role of perinephric fat invasion more accurately in patients with localized RCC, we have excluded patients with lymph node involvement. In this study, we have found perinephric fat invasion as an independent prognostic factor together with tumor grade, which is consistent with Siddiqui and colleagues' study.[8] The 7 cm cutoff value for tumor size was not found to be an independent prognostic factor. This finding disagrees with the outcomes of Siemer,[7] Yoo,[9] and Murphy[12] studies.

Gofrit and associates emphasized the heterogeneity of pT3a tumors and represented perinephric fat invasion as an insignificant prognostic factor. They have proposed a new TNM staging system, which excludes perinephric fat invasion and applies only tumor size and venous involvement. This inference is contrary to our results since perinephric fat invasion was an independent prognostic factor in our series. The shared opinion of these authors is the prominent role of the tumor size on prognosis.[13]

In our study, the 7 cm cutoff value provided prognostic stratification only in patients with pT3a. Patients staged as pT2 and pT3a ≤7 cm did not display any significant DSS differences. The DSS of patients with pT3a tumors >7 cm was found to be significantly inferior to patients with pT2 and pT3a tumors ≤7 cm. This data verifies the outcomes of

Lam and coworkers.[14] They suggested the consideration of adjuvant treatment in patients with pT3a >7 cm because of the significantly decreased DSS in those patients. These outcomes were confirmed by Yoo and colleagues as well.[9] We have also exhibited the significant difference in DSS between patients with pT1 and pT3a ≤7 cm. However, Yoo and associates did not report any significant difference between these groups.[9] Roberts and coworkers also showed similar prognosis pattern in patients with pT1 and pT3a ≤ 7 cm.[15] The univariate and multivariate analyses did not demonstrate any negative impact of perinephric fat invasion on DSS in patients with tumor size ≤4 cm. On the other hand, other tumor size groups were affected by perinephric fat invasion. Our results differ from Siddiqui and colleagues' study only in patients with tumor size ≤4 cm.[8]

Our study was not without limitations. Although the medical records of patients were carefully examined, retrospective feature of this study and the relatively small number of patients in the pT3a group (n = 63) are disadvantages. Thus, only patients with pT1-3aN0M0 RCC were included. One major advantage of our study was the evaluation of the pathological specimens by a single and experienced pathologist.

CONCLUSION

Although perinephric fat invasion is an accepted prognostic factor alone, employing tumor size will strengthen the efficacy in TNM staging system and help to differentiate patient subgroups with diverse DSS. Our results pointed out that tumor size should be applied in patients with pT3a RCC for more accurate prognostic evaluation. However, prospective studies are needed for higher level of evidence.

CONFLICT OF INTEREST

None declared.

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