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The Prognostic Implications of Cystic Change in Clear Cell Renal Cell Carcinoma

Heae Surng Park · Eun-Jung Jung
Jae Kyung Myung
Kyung Chul Moon[1]

Department of Pathology, Seoul National University College of Medicine; [1]Kidney Research Institute, Medical Research Center, Seoul National University College of Medicine, Seoul, Korea

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Corresponding Author
Kyung Chul Moon, M.D., Ph.D.
Department of Pathology and Kidney Research Institute, Medical Research Center, Seoul National University College of Medicine, 28 Yeongeon-dong, Jongno-gu, Seoul 110-799, Korea
Tel: 02-2072-1767
Fax: 02-743-5530
E-mail: blue7270@snu.ac.kr

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Background : Cystic renal cell carcinoma has been reported to have a good prognosis. However, previous studies included cases of multilocular cystic renal cell carcinoma, which has an excellent prognosis, and renal cell carcinoma with cystic necrosis, which has an adverse prognosis. Therefore, we analyzed the prognostic influence of cystic change in clear cell renal cell carcinoma after excluding those morphological features. **Methods :** We identified 225 patients with clear cell renal cell carcinoma who underwent nephrectomy between 2001 and 2003. The clinicopathologic features were compared with clinical outcomes. **Results :** Cystic change in clear cell renal cell carcinoma (n = 66) was significantly associated with younger patient age (< 55), smaller tumor size (≤ 4 cm), lower pT stage (pT1, T2), M0 stage at initial diagnosis, lower tumor, node, and metastasis stage (I, II), and lower nuclear grade (1, 2). Patients with cystic change in clear cell renal cell carcinoma had significantly longer cancer-specific (p = 0.015) and progression-free survival (p = 0.004) than those without cystic change, by univariate analysis. Multivariate analysis revealed that cystic change significantly decreased the risk of cancer progression (risk ratio, 0.27; 95% confidence interval, 0.11 to 0.69). **Conclusions :** In patients with clear cell renal cell carcinoma, cystic change is a good independent predictor for survival.

Key Words : Carcinoma, renal cell; Prognosis; Pathology

The incidence of renal cancers has been increasing steadily with 57,760 new diagnoses and 12,980 deaths in the United States in 2009.[1] Renal cell carcinoma (RCC) accounts for approximately 75% of these cases[2] and clear cell type is the most common histologic variant. Clear cell RCC is associated with poorer cancer-specific survival (CSS) when compared with other subtypes.[3] However, multilocular cystic renal cell carcinoma (MCRCC), a distinct subtype of clear cell RCC, has excellent prognosis with a 5-year survival rate of 95% to 100%.[4-6] Some studies reported that patients with cystic RCC, a category that includes MCRCC, unilocular cystic RCC, RCC with extensive cystic necrosis, and cystic RCC characterized by a unilocular cyst with one or a few isolated mural tumor nodules, had a better prognosis than patients with solid clear cell RCC.[7-11] These studies should be clarified since RCC with cystic necrosis carries a significantly worse prognosis[12] and MCRCC has an excellent outcome. Therefore, we performed a retrospective analysis to assess the prognostic implication of cystic change in clear cell RCC after excluding those confounding factors.

MATERIALS AND METHODS

Patient selection

We reviewed the pathology slides of patients treated with radical or partial nephrectomy for clear cell RCC between 2001 and 2003 at the Seoul National University Hospital. MCRCC or cases showing equivocal features for the diagnosis of typical clear cell RCC, such as papillary architecture and tumor cells with clear cytoplasm, reminiscent of clear cell papillary RCC[13] were excluded. To diagnose MCRCC, we applied strict criteria based

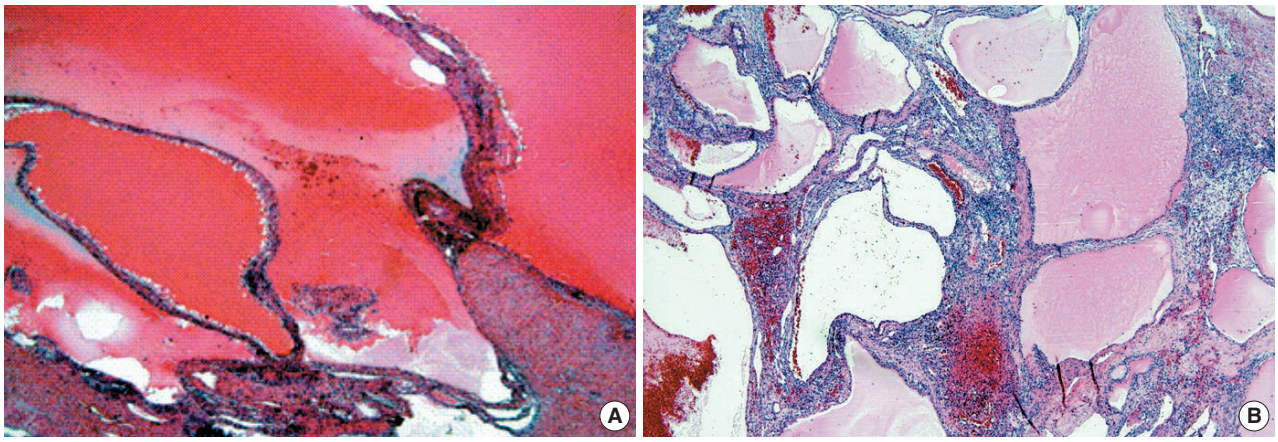

Fig. 1. Histologic appearance of cystic change in clear cell renal cell carcinoma compared to multilocular cystic renal cell carcinoma. (A) A multilocular cystic renal cell carcinoma excluded from this study. (B) Clear cell renal cell carcinoma with cystic change. Usually, the cystic area appears as macrocysts in a multilocular pattern. The lumen contains serous fluid and erythrocytes, but not necrotic tissue. There is expansile tumor mass in the cyst walls.

on the 2004 World Health Organization (WHO) classification.[14] MCRCC was defined as the tumor mass entirely composed of multilocular cysts lined by thin septa containing clear tumor cells, and with no expansile solid nodule (Fig. 1A). Finally, the cases of 225 patients with clear cell RCC were examined for analysis.

Collection of clinicopathologic features

The clinical features included age at the time of surgery, sex and clinical outcomes. The duration of follow-up was calculated from the date of nephrectomy to the date of cancer progression (i.e., distant metastases after nephrectomy for the primary tumor), death, or last follow-up. The pathologic features evaluated included tumor size, tumor, node, and metastasis (TNM) stage according to the 2002 American Joint Committee on Cancer (AJCC),[15] regional lymph node involvement, distant metastases, nuclear grade according to the Fuhrman system, and cystic change. If no pathologic confirmation of metastatic disease was performed, patients were assessed for clinical metastatic stage on the basis of clinical examination and radiologic studies. Tumor size was measured according to the longest diameter. Nuclear grade was based on the highest-grade tumor area identified. A tumor was regarded as having cystic change when it was grossly cystic and the cyst walls were lined by clear tumor cells. Cysts were either multilocular or unilocular and there was at least one area of expansile tumor nodule, which differentiated the tumor from MCRCC. In addition, the cysts could not contain necrotic tumor tissue. Usually, the cystic area consisted of macrocysts in a multilocular pattern with the lumens containing serous fluid and erythrocytes (Fig. 1B). Microscopic slides from all specimens were reviewed by two pathologists without knowledge of patient outcomes.

Statistical methods

Comparisons of clinical and pathologic features between clear cell RCC patients with and without cystic change were assessed using chi-square and Fisher exact tests. CSS was measured from the date of surgery to the date of cancer-related death or the last follow-up. Progression-free survival (PFS) was calculated from the date of surgery to the date of tumor recurrence/metastasis or the last follow-up. Survival analysis was performed using the Kaplan-Meier method and the results were compared by the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression models. Statistical analyses were performed using the SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). All p-values of 0.05 or less were considered statistically significant.

RESULTS

The clinical and pathologic features for the 225 patients who underwent nephrectomy for clear cell RCC are summarized in Table 1. The mean age at the time of surgery was 55 years (range, 28 to 82 years). The mean duration of follow-up was 59.96 months (median, 64.0 months; range, 2 to 97 months). Of the 225 patients, 45 (20%) patients died during the follow-up, with 33 (14.7%) dead of disease. One hundred and sixty-three

Table 1. Clinicopathologic features of 225 patients who underwent nephrectomy for clear cell renal cell carcinoma

Features		Value	%
Age at the time of surgery (yr)			
	Mean ± SD	55.0 ± 11.2	
	Median	55	
	Range	28-82	
Tumor size (cm)			
	Mean ± SD	5.1 ± 3.1	
	Median	4	
	Range	1-16	
Sex			
	Female	54	24
	Male	171	76
Age category (yr)			
	< 55	116	51.5
	≥55	109	48.5
Tumor size (cm)			
	≤ 4	114	50.7
	> 4	111	49.3
Primary tumor status[a]			
	pT1	158	70.2
	pT2	28	12.4
	pT3	38	16.9
	pT4	1	0.4
Regional lymph nodes status[a]			
	N0	221	98.2
	N1, N2	4	1.8
Distant metastasis[a]			
	M0	205	91.1
	M1	20	8.9
TNM stage[a]			
	I	155	68.9
	II	22	9.8
	III	26	11.6
	IV	22	9.8
Fuhrman nuclear grade			
	1	22	9.8
	2	104	46.2
	3	76	33.8
	4	23	10.2
Cystic change			
	Absent	159	70.7
	Present	66	29.3

[a] According to American Joint Committee on Cancer TNM staging system.[15]
SD, standard deviation; TNM, tumor, node, and metastasis.

(72.4%) patients were alive without evidence of RCC, and 17 (7.6%) patients were currently alive with evidence of disease. Grossly, the mean tumor size was 5.1 cm (range, 1 to 16 cm). One hundred and eleven (49.3%) patients had tumor masses greater than 4 cm in size.

Cystic change in clear cell RCC was observed in 66 (29.3%) patients (Table 1). Its associations with clinicopathologic features are summarized in Table 2. It was significantly associated with

Table 2. Relationship of the presence of cystic change within clear cell renal cell carcinoma to clinicopathologic features

Clinicopathologic features	Cystic change		p-value
	Absent n (%)	Present n (%)	
Sex			0.188
Female	42 (26.4)	12 (18.2)	
Male	117 (73.6)	54 (81.8)	
Age (yr)			< 0.001
< 55	70 (44.0)	46 (69.7)	
≥55	89 (56.0)	20 (30.3)	
Tumor size (cm)			0.029
≤4	73 (45.9)	41 (62.1)	
> 4	86 (54.1)	25 (37.9)	
Primary tumor status[a]			0.035
pT1, T2	126 (79.2)	60 (90.9)	
pT3, T4	33 (20.8)	6 (9.1)	
Regional lymph nodes status[a]			0.19
N0	155 (97.5)	66 (100)	
N1, N2	4 (2.5)	0	
Distant metastasis[a]			0.04
M0	141 (88.7)	64 (97.0)	
M1	18 (11.3)	2 (3.0)	
TNM stage[a]			0.011
I and II	118 (74.2)	59 (89.4)	
III and IV	41 (25.8)	7 (10.6)	
Fuhrman nuclear grade			0.038
1 and 2	82 (51.6)	44 (66.7)	
3 and 4	77 (48.4)	22 (33.3)	

[a] According to American Joint Committee on Cancer TNM staging system.[15]
TNM, tumor, node, and metastasis.

patient age less than 55 years old ($p < 0.001$), tumor size 4 cm or less ($p = 0.029$), less advanced primary tumor status ($p = 0.035$), absence of distant metastases at initial diagnosis ($p = 0.04$), lower TNM stage ($p = 0.011$), and lower Fuhrman nuclear grade ($p = 0.038$) (Table 2).

Univariate analysis showed that patients with age younger than 55 years old (CSS, $p = 0.001$; PFS, $p < 0.001$), tumor size 4 cm or less ($p < 0.001$), less advanced primary tumor status ($p < 0.001$), absence of regional lymph node ($p < 0.001$), abscence of distant metastasis ($p < 0.001$), lower TNM stage ($p < 0.001$), and lower Fuhrman nuclear grade ($p < 0.001$) were significantly associated with longer CSS and PFS (Table 3). Tumors with cystic change were also correlated with longer survival (CSS, $p = 0.015$; PFS, $p = 0.004$) (Fig. 2).

Multivariate analysis determined the following independent prognostic factors for CSS as well as for PFS in this study, as follows: tumor size 4 cm or less (CSS, $p = 0.032$; PFS, $p = 0.002$), primary tumor status (CSS, $p = 0.005$; PFS, $p = 0.005$), regional lymph node status (CSS, $p = 0.037$; PFS, $p = 0.013$), distant

metastasis (both CSS and PFS, p < 0.001), and Fuhrman nuclear grade (CSS, p = 0.013; PFS, p = 0.008) (Table 4). Although cystic change did not retain prognostic significance for cancer-related death by multivariate analysis, it significantly decreased the risk of cancer progression regardless of other clinicopathologic parameters (risk ratio [RR], 0.27; 95% confidence interval [CI], 0.11 to 0.69; p = 0.006).

Table 3. Univariate analysis of clinicopathologic factors in 225 patients with clear cell renal cell carcinoma

Clinicopathologic features	Cancer specific survival p-value	Progression free survival p-value
Age (yr) < 55 vs ≥ 55	0.001	< 0.001
Tumor size (cm) ≤ 4 vs > 4	< 0.001	< 0.001
pT1, pT2 vs pT3, pT4	< 0.001	< 0.001
pN0 vs pN1, pN2	< 0.001	< 0.001
pM0 vs pM1	< 0.001	< 0.001
Stage I, II vs III, IV	< 0.001	< 0.001
Nuclear grade 1, 2 vs 3, 4	< 0.001	< 0.001
Cystic change absent vs present	0.015	0.004

DISCUSSION

Imaging studies reveal cystic changes in 4% to 15% of renal cell carcinomas.[16] In 1986, Hartman *et al*.[16] divided these tumors into 4 groups to explain their cystic nature: intrinsic multilocular growth, intrinsic unilocular growth, cystic necrosis, and origin from the epithelial lining of a pre-existing cyst. Several

Table 4. Multivariate analysis for cancer-specific and progression-free survival

Feature	Cancer-specific survival		Progression-free survival	
	RR (95% CI)	p-value	RR (95% CI)	p-value
Age (yr) < 55 vs ≥ 55	0.65 (0.26-1.61)	0.35	1.06 (0.54-2.10)	0.865
Tumor size (cm) ≤ 4 vs > 4	9.53 (1.21-74.90)	0.032	5.57 (1.89-16.42)	0.002
pT1, T2 vs pT2, T3	2.98 (1.40-6.35)	0.005	2.46 (1.31-4.61)	0.005
N0 vs N1, N2	3.69 (1.08-12.55)	0.037	5.55 (1.44-21.41)	0.013
M0 vs M1	11.08 (4.95-24.80)	< 0.001	13.63 (5.99-31.00)	< 0.001
Nuclear grade 1, 2 vs 3, 4	3.97 (1.34-11.78)	0.013	2.85 (1.32-6.15)	0.008
Cystic change absent vs present	0.34 (0.11-1.04)	0.058	0.27 (0.11-0.69)	0.006

RR, risk ratio; 95% CI, 95% confidence interval.

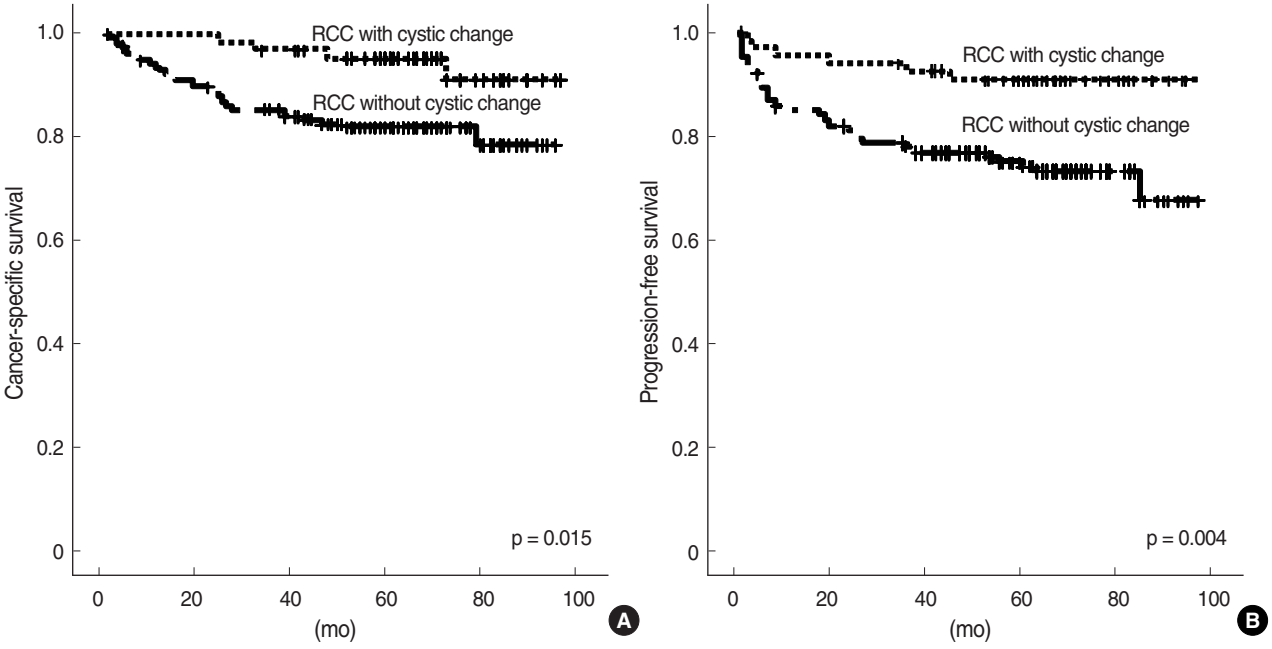

Fig. 2. Kaplan-Meier survival curves according to the presence of cystic change in 225 patients with clear cell renal cell carcinoma (RCC). (A) Cancer-specific survival (log-rank test for trend, p = 0.015). (B) Progression-free survival (log rank test for trend, p = 0.004).

authors have reported that such "cystic RCC" had a more favorable prognosis than noncystic RCC.[7-11] Bielsa *et al*.[7] and Webster *et al*.[11] demonstrated that survival was significantly longer in patients with cystic RCC. In these studies, some cases of cystic RCC with multilocular growth pattern might now be categorized as multilocular cystic RCC by the 2004 WHO classification of the renal tumors.[14] MCRCC is composed entirely of cysts of varying sizes lined by a single layer of neoplastic cells and without an expansile tumor nodule. It must be distinguished from conventional RCC with cystic change, since it has an extremely good prognosis[5] and currently is considered as a specific entity, "multilocular cystic renal neoplasm of low malignant potential".[17] Consequently, those previous studies may have overestimated the prognosis of patients with cystic RCC. Furthermore, some studies also included RCC with cystic necrosis and this could act as a confounding factor contributing to the underestimation of clinical outcome. Consequently, we excluded cases of MCRCC in the current study and did not consider areas of cystic necrosis as cystic change. This is the first study that statistically evaluated the prognostic impact of cystic change in clear cell RCC excluding cases with MCRCC and RCC with cystic necrosis.

The TNM staging system is the most studied and most accurate tool for predicting the prognosis of RCC.[18] Our study was in close agreement with the results of previous studies in spite of the relatively small population size. Because the outcomes of RCC can still be unpredictable, other prognostic factors and outcome prediction models have been studied. The current version of the TNM staging system uses a 4 cm cut-off value to distinguish between T1a and T1b RCC. Several authors have suggested different tumor size cut-off ranging from 4.5 cm to 5.5 cm.[19] In this study, we adopted 4 cm as a tumor size breakpoint for stratifying the patients and showed that tumor sizes greater than 4 cm significantly increased the risk of cancer mortality (RR, 9.53; 95% CI, 1.21 to 74.90; p = 0.032) and progression (RR, 5.57; 95% CI, 1.89 to 16.42; p = 0.002) by multivariate analysis. Fuhrman nuclear grade has been shown to be of prognostic significance in series of mixed tumor types.[3,20,21] However, using 4-tiered system, it did not retain prognostic significance by multivariate analysis that included TNM stage.[20] On the other hand, significant differences in outcome were seen after separating patients with nuclear grade 1 and grade 2 tumors from patients with grade 3 and grade 4 tumors.[22] Our study also showed that nuclear grade maintained prognostic significance only after grouping patients into 2-tiered system (grade 1 and 2 vs grade 3 and 4). We demonstrated that cystic change in clear cell RCC was significantly associated with patient age younger than 55 years old and less aggressive properties as follows: tumor size 4 cm or less, less advanced primary tumor status, absence of distant metastases at initial diagnosis, lower TNM stage, and lower Fuhrman nuclear grade. By univariate analysis, cystic change was significantly associated with longer survival (CSS, p = 0.015) and less intensive disease progression (PFS, p = 0.004). After adjustment for tumor size, primary tumor status, regional lymph node status, distant metastasis, and Fuhrman nuclear grade, clear cell RCC with cystic change exhibited a significantly decreased likelihood of cancer progression (RR, 0.27; p = 0.006). Therefore, the presence of cystic architecture in clear cell RCC, when grossly detected and then microscopically confirmed, is a good independent predictor for cancer progression, even if the cystic portion is not large enough to diagnose multilocular cystic RCC. Additional studies with large population size are needed to clarify the definition of cystic change and to better understand its impact on cancer mortality.

In conclusion, clear cell RCC with cystic change was found to be significantly associated with more favorable clinicopathologic parameters than noncystic RCC. In addition, the presence of cystic architecture in clear cell RCC was identified as an independent predictor of PFS by multivariate analysis. Routine documentation of cystic change may be advisable during the pathologic assessment of RCC.

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