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Brief communication (Original)

Correlation of computed tomography characteristics of cystic renal cell carcinoma with histopathology

Pattarin Burapasomboon, Piyaporn Boonsirikamchai, Kewalee Sasiwimonphan
Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Background: Renal cysts are common incidental findings in computed tomography (CT) of the abdomen and range from benign to cystic renal cell carcinoma (RCC). Cystic RCC has various pathology, clinical prognosis, and treatment options.
Objectives: To compare preoperative CT of cystic RCC with histopathology.
Methods: Preoperative CT of histopathologically proven cystic RCCs were retrospectively reviewed in this single-center cross-sectional observational study. Two investigators recorded consensus CT features for each cystic RCC. The means of descriptive continuous data were calculated. A chi-square test, Fisher's exact test, or an ANOVA were used for compare the frequency of findings for each histopathological subtype.
Results: Of 38 cystic RCCs, 25 were clear cell RCC, 5 were papillary RCC, 4 were multilocular cystic RCC, 1 was chromophobe RCC, and 3 were mixed type/other type (papillary/chromophobe, clear cell/chromophobe, and sarcomatoid type). We classified 36 lesions as Bosniak category IV and 2 lesions as Bosniak category III. There was no significant difference in cyst attenuation in any phase. Solid attenuation of the tumors was significantly different for each type in corticomedullary and nephrogenic phases (P = 0.001 and 0.042, respectively). Clear cell RCC was enhanced the most on corticomedullary and nephrogenic phases (means 135.5 and 112.1 Hounsfield Units, respectively). Septal thickening, enhancement, and multilocularity were significantly different between subtypes, particularly in multilocular cystic RCCs (P = 0.018, 0.018, and 0.02, respectively).
Conclusion*:* Preoperative CT findings may help clinicians and radiologists to predict tumor subtypes and aid treatment planning.

Keywords: Computed tomography, cystic renal cell carcinoma, histopathology

Renal cysts are common in the general population and are commonly recognized in abdominal computed tomography (CT). CT allows us to appreciate the frequency of renal cysts in the general population, which are estimated to occur in at least 50% of all people older than 50 years [1]. The great majority of cases are cysts in the kidney discovered incidentally when the patient has undergone CT for some other reason [2].

The criteria for diagnosis of a simple cyst using CT are a sharp margin and demarcation from the surrounding renal parenchyma, a smooth and thin wall, homogeneous water density content (0-20 Hounsfield Units (HU)), and no enhancement following intravenous administration of contrast material. When all imaging criteria for a simple cyst are present, they have been shown to have a negligible likelihood of malignancy. However, simple cysts are complicated with hemorrhage, infection, inflammation, or ischemia. The complicated cyst may demonstrate calcification, hemorrhage, septation, wall thickening, nodularity, or a combination of these features at gross inspection.

Approximately 10% of cases of renal cell carcinoma (RCC) manifest primarily as a fluid-filled cystic mass. Cystic RCC demonstrates features identical to those of a complicated cyst from gross inspection. Therefore, definitive differentiation between a complicated cyst and a cystic RCC requires histological examination [3].

The best method for cure of RCC is complete excision or ablation of the primary malignancy before it has metastasized. Various studies have described better clinical outcomes and survival rates for cystic RCCs. Patients with cystic RCCs are less likely to present with symptoms, have smaller tumors, and are respond well to less-aggressive treatment strategies [4-7].

The goal of RCC treatment is preservation of renal function without compromising the oncological outcome, and possibility of considering nephron-

Correspondence to: Kewalee Sasiwimonphan, Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: kewalee.s@chula.ac.th

sparing surgery for these subtypes. If CT findings can predict a histopathological subtype, particularly multilocular cystic RCC, which has a very good prognosis, the surgeon may perform nephron-sparing surgery in selected patients [7].

The purpose of this study was to evaluate the preoperative radiological CT characteristics of cystic RCC and to correlate these characteristics with histopathological findings, which may aid less invasive surgery in selected patients.

Materials and methods

Patient population

This was a retrospective single-center observational study of a cross-section of patients. The Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University (Bangkok, Thailand) reviewed the protocol for and approved this study (certificate of approval No. 662/2014, IRB No. 380/57). We reviewed the medical records and electronic database of King Chulalongkorn Memorial Hospital to identify patients with a diagnosis of RCC from January 1, 2007 to September 30, 2014, and patients who undergone nephrectomy from 2007 to 2013. We initially identified 598 patients.

Inclusion and exclusion criteria

For inclusion, we required preoperative cross-sectional CT imaging of the upper abdomen or whole abdomen with at least precontrast and intravenous contrast CT, which included a precontrast, corticomedullary phase, and nephrogenic phase. The preoperative CT must have been recorded on our picture archiving and communication system (PACS). All of the selected cases must have had a histopathological diagnosis of RCC according to the WHO 2004 criteria. Adequate preoperative CT scan recorded on PACS and histopathological records were available in 217 of 598 cases (36%).

Definition of cystic RCC

Cystic RCCs were defined in imaging as: well-defined lesions with predominantly low attenuation (≤20 HU) in precontrast CT, predominantly cystic lesions with high attenuation (40–70 HU) without enhancement (proteinaceous or hemorrhagic cysts), or mixed cystic/solid lesion, in which the cystic component was >50%. Septum and wall thickening was defined as thickness ≥2 mm. Septal, wall, and nodular enhancement were defined by different density in pre- and postcontrast images >15 HU.

CT protocol

This study included CT of the upper abdomen or whole abdomen, and included at least a precontrast scan and post intravenous contrast or CT scan of the upper abdomen or whole abdomen including a precontrast, corticomedullary phase, and nephrogenic phase. We used a Siemens Somatom Sensation plus 4 or 16 (Siemens Medical Solutions, Erlangen, Germany) or GE 750 scanner (GE Medical Systems, Waukesha, WI, USA) in the Department of Radiology, King Chulalongkorn Memorial Hospital. For this study, the Somatom Sensation 16 system used a 16 mm × 0.75 mm collimator, 24.0 mm feed per rotation and 0.5 s rotation time (140 mA, 120 kVp, and pitch = 1 mm/rotation). For the GE 750 system we used a 0.625 mm × 64 mm collimator, rotation time = 0.5 s (mA ranging: min = 100 max, 120 kV, pitch 1.375:1 mm/rotation).

Image analysis

From 217 cases, 182 (83.9%) were solid RCC and 35 cases (16.1%) were cystic RCC according to preoperative imaging. There were 3 patients who had 2 synchronous cystic RCCs in preoperative imaging, so there are 38 lesions for characterization. Two investigators; including a radiologist (KS with 7 years' experience in genitourinary imaging) and a resident training in diagnostic radiology (PB with 3 years' experience in radiology) were blinded to clinical data and reviewed preoperative imaging independently. The 2 investigators reviewed the images again together to reach a final consensus.

The following features of each cystic RCC were recorded: density of renal parenchyma, location (left or right kidney, and upper middle or lower pole); tumor size; diffuse wall or septal thickness of 2 mm or greater; presence of focal wall or septal thickening; presence and size of nodules; presence and size of calcifications; density of the cyst; and enhancement of the wall, septum, or nodule; presence of multilocularity of cyst and Bosniak's classification of the cystic RCCs. Tumor size was measured at its longest diameter using a caliper tool on the PACS. The degree of enhancement was evaluated by the mean value of attenuation measurement of regions of interest (ROIs). The ROIs were obtained by assignment of a 1 cm^2 round or elliptical ROI cursor over the enhanced area in postcontrast or excretory phase. The degree of enhancement of both normal renal parenchyma and tumor were also measured by the method described above.

Statistical analysis

All data from selected cases were summarized as descriptive nominal data and presented as a percentage of each CT finding. All descriptive continuous data were calculated as mean values. A chi-square test, Fisher exact test, or ANOVA were used to compare the frequency of findings for each histopathological subtype. Statistical significance was defined as $P < 0.05$. We performed all calculations using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA).

Results

Demographic data

The demographic data from all the patients with cystic RCC were as follows: most frequent stage at diagnosis is stage 1 = 14 lesion (37%), stage 2 = 3 lesions (8%), stage 3 = 13 lesions (34%), and stage 4 = 8 lesions (21%). Most frequent surgical intervention was radical nephrectomy, followed by tissue biopsy, or partial nephrectomy (**Table 1**). There were 2 patients who had underlying von Hippel–Lindau disease.

Histopathological subtype

The most common subtype of cystic RCC found in our study was clear cell RCC. The other subtypes are papillary RCC (5 lesions, 13.2%), multilocular cystic RCC (4 lesions, 10.5%), chromophobe RCC (1 lesion, 2.6%) and mixed type/other subtype (3 lesions, 7.9%; papillary/chromophobe = lesion, clear cell/chromophobe = 1 lesion and sarcomatoid type = 1 lesion) (**Table 2**).

CT findings of cystic RCC

We investigated 38 cystic RCC lesions during this period. Mean tumor diameter was 7.1 cm (1.5–6.9 cm). The stage at diagnosis in each tumor subtypes is described in **Table 3**. We also classified all cystic RCCs using Bosniak's classification. Almost tumors were classified into Bosniak category IV. Only 2 lesions of clear cell RCC were Bosniak category III (**Table 4**).

There was no significant difference in mean renal parenchymal attenuation in precontrast CT of each tumor subtype. There was no significant difference in cyst attenuation of each tumor subtype in precontrast phase, corticomedullary phase, and nephrogenic phase. Solid attenuation of the tumor showed a significant difference in each subtype on both corticomedullary and nephrogenic phases. Clear cell RCC showed highest enhancement on both corticomedullary (mean HU = 135.5) and nephrogenic phases (mean HU = 112.1). While, the least enhancing tumor on both corticomedullary (mean HU = 59.4) and nephrogenic phases (mean HU = 71.8) was papillary RCC (**Table 5, Figures 1–3**).

Presence of septal thickening, septal enhancement, and multilocularity were shown to be significantly different findings among subtypes of cystic RCCs in our study, particularly multilocular cystic RCC. All multilocular cystic RCCs showed the presence of septal thickening, septal enhancement, and multilocularity (**Figure 4**). Wall thickening, wall enhancement, nodular enhancement and calcification failed to demonstrate significant difference between the tumor subtypes (**Tables 6 and 7**).

Table 1. Demographic data

Clinical data	Outcome
Number of cases	38 lesions (35 patients)
Sex	
Male	33 (87%)
Female	5 (13%)
Male: female ratio	6.6
Age, mean (range) years	58.84 years (23-87)
Type of surgery	
Radical nephrectomy	27 (71%)
Tissue biopsy	8 (21%)
Partial nephrectomy	3 (8%)

Table 2. Histopathologic subtypes of renal cell carcinoma (RCC)

Histopathologic subtype	Number (lesion)	Percentage
Clear cell RCC	25	66%
Papillary RCC	5	13%
Multilocular cystic RCC	4	11%
Chromophobe RCC	1	3%
Mixed type/other subtype*	3	8%

* = papillary/chromophobe = 1, clear cell/chromophobe = 1, sarcomatoid type = 1

Table 3. Stage at diagnosis and histopathologic subtypes of renal cell carcinoma (RCC)

Histopathology	Stage at diagnosis (%)				Total
	1	2	3	4	
Clear cell RCC	10	3	9	3	25
Papillary RCC	1	0	1	3	5
Multilocular cystic RCC	3	0	1	0	4
Chromophobe RCC	0	0	1	0	1
Mix subtype	0	0	1	2	3
Total	14 (37)	3 (8)	13 (34)	8 (21)	38 (100)

Table 4. Bosniak's classification of renal cell carcinoma (RCC)

Subtype	III (% in subtype)	IV (% in subtype)
Clear cell RCC	2 (8%)	23 (92%)
Papillary RCC	0 (0%)	5 (100%)
Multilocular cystic RCC	0 (0%)	4 (100%)
Chromophobe RCC	0 (0%)	1 (100%)
Mix type/other subtype	0 (0%)	3 (100%)

Table 5. Parenchymal, cystic, and solid tumor attenuation (Hounsfield Units) of renal cell carcinomas (RCCs)

Findings types	Clear cell RCC	Papillary RCC	Multilocular cystic RCC	Chromophobe RCC	Mix-type RCC	*P*
Renal parenchymal attenuation (mean)						
Precontrast	33.6	36.0	34.0	26.3	33.3	0.51
Cyst attenuation (mean)						
Precontrast	21.3	22.6	12.3	21.8	17.8	0.446
Corticomedullary phase	28.0	28.4	17.3	23.6	20.3	0.66
Nephrogenic phase	28.2	26.2	26.3	19.3	21.3	0.86
Solid attenuation (mean)						
Precontrast	37.2	36.0	27.3	37.8	40.0	0.27
Corticomedullary phase	135.5	59.4	85.8	81.5	99.0	0.001
Nephrogenic phase	112.1	71.8	92.8	82.2	86.3	0.042

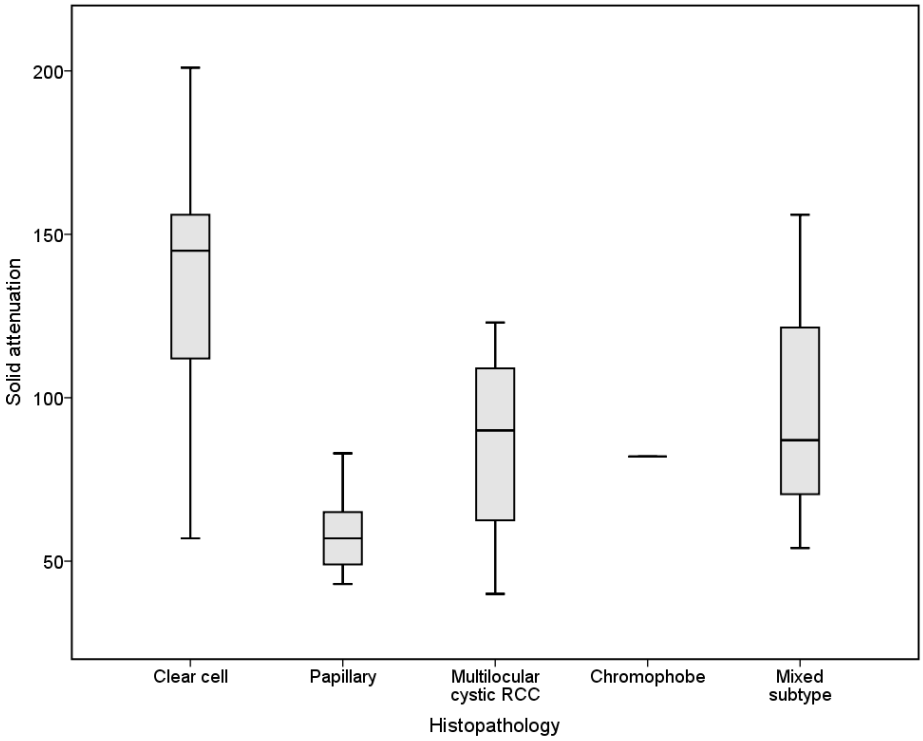

Figure 1. Attenuation of the solid part of tumor in the corticomedullary phase in each subtype is shown in these box plots. Median values are indicated by the central bar. Box indicates the 95% confidence intervals and the whiskers indicate maximum and minimum values. Clear cell renal cell carcinoma (RCC) was the most enhancing tumor subtype in the corticomedullary phase. The least enhancing subtype was papillary RCC ($P = 0.001$).

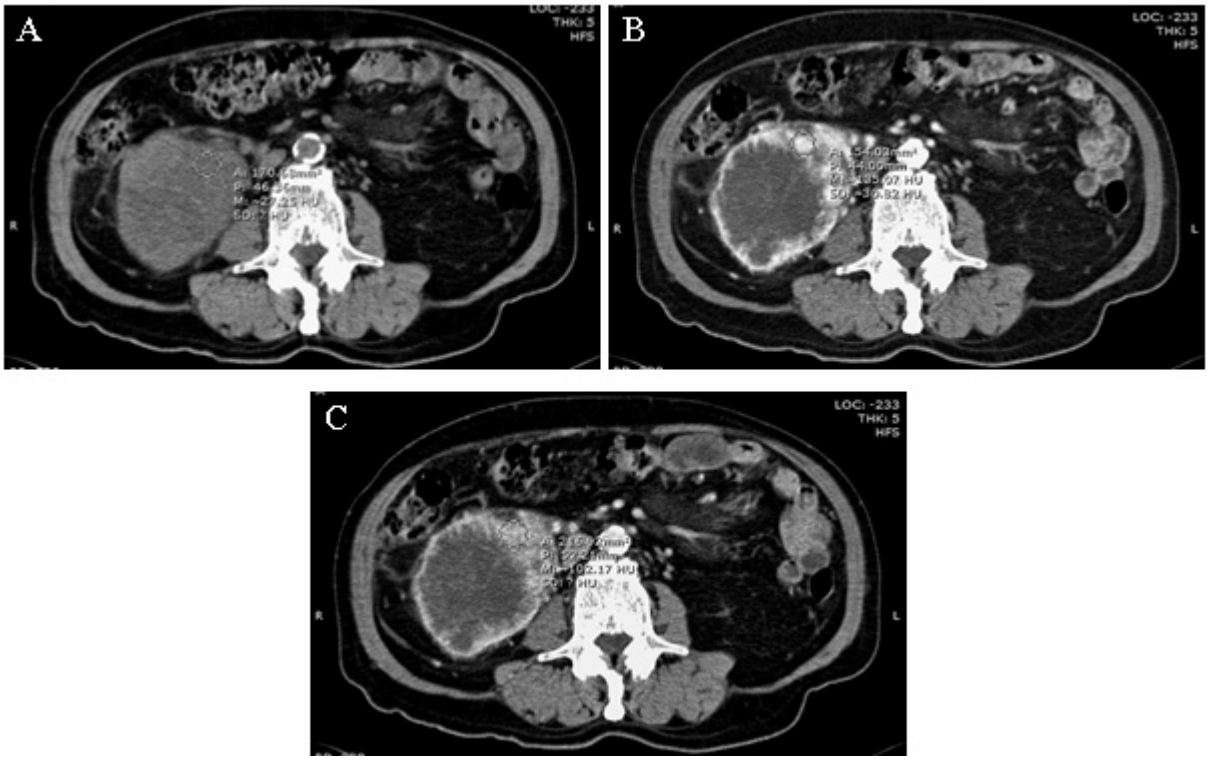

Figure 2. Images from a 78-year-old man with clear cell renal cell carcinoma at the right kidney. Axial precontrast (**A**), corticomedullary phase (**B**), and nephrogenic phase (**C**) images. **A.** Precontrast CT: A 9.0 cm × 6.0 cm mixed solid-cystic lesion at lower pole of right kidney (HU 27.3). **B.** Corticomedullary phase: peripheral enhancing solid portion (HU 135.1) with central nonenhancing cystic component. **C:** Nephrogenic phase: persistent intense enhancement of solid portion (HU 102.2). The patient underwent a radical right nephrectomy. Clear cell renal cell carcinoma was proven from the histopathology.

Figure 3. Images from a 52-year-old man with right renal cystic mass. Axial precontrast (**A**), corticomedullary phase (**B**) and nephrogenic phase (**C**) images. **A.** Precontrast CT: a 3.1 cm × 3.4 cm well-defined cystic lesion at the lower pole of right kidney (Hounsfield Units (HU) 24.6). **B.** Corticomedullary phase: small enhancing solid mural nodule (HU 62.3). **C.** Nephrogenic phase: delayed enhancement of solid mural nodule. (HU 72.02). Radical right nephrectomy was performed. Pathology is papillary renal cell carcinoma.

Table 6. Computed tomography of septal thickening and enhancement; wall thickening and enhancement, nodular enhancement, multilocularity, and calcification of renal cell carcinomas (RCCs)

Finding/ types	Clear cell RCC	Papillary RCC	Multilocular cystic RCC	Chromophobe RCC	Mix-type RCC	*P*
Septal thickening						
absence	18	1	0	0	1	
presence	7	4	4	1	2	0.02
Septal enhancement						
absence	18	1	0	0	1	
presence	7	4	4	1	2	0.02
Wall thickening						
absence	12	2	0	1	1	
presence	13	3	4	0	2	0.32
Wall enhancement						
absence	12	1	0	1	1	
presence	13	4	4	0	2	0.22
Nodular enhancement						
absence	21	3	4	1	2	
presence	4	2	0	0	1	0.52
Multilocularity						
absence	18	1	0	1	1	
presence	7	4	4	0	2	0.02
Calcification						
absence	15	4	4	1	2	
presence	10	1	0	0	1	0.49

Table 7. Computed tomography of septal thickening, septal enhancement, and multilocularity compared between nonmultilocular cystic renal cell carcinoma (RCC) and multilocular cystic RCC subtypes

Findings/ types	Nonmultilocular cystic RCC	Multilocular cystic RCC	*P*
Septal thickening/enhancement			
absence	20	0	
presence	14	4	0.053
Multilocularity			
absence	21	0	
presence	13	4	0.04

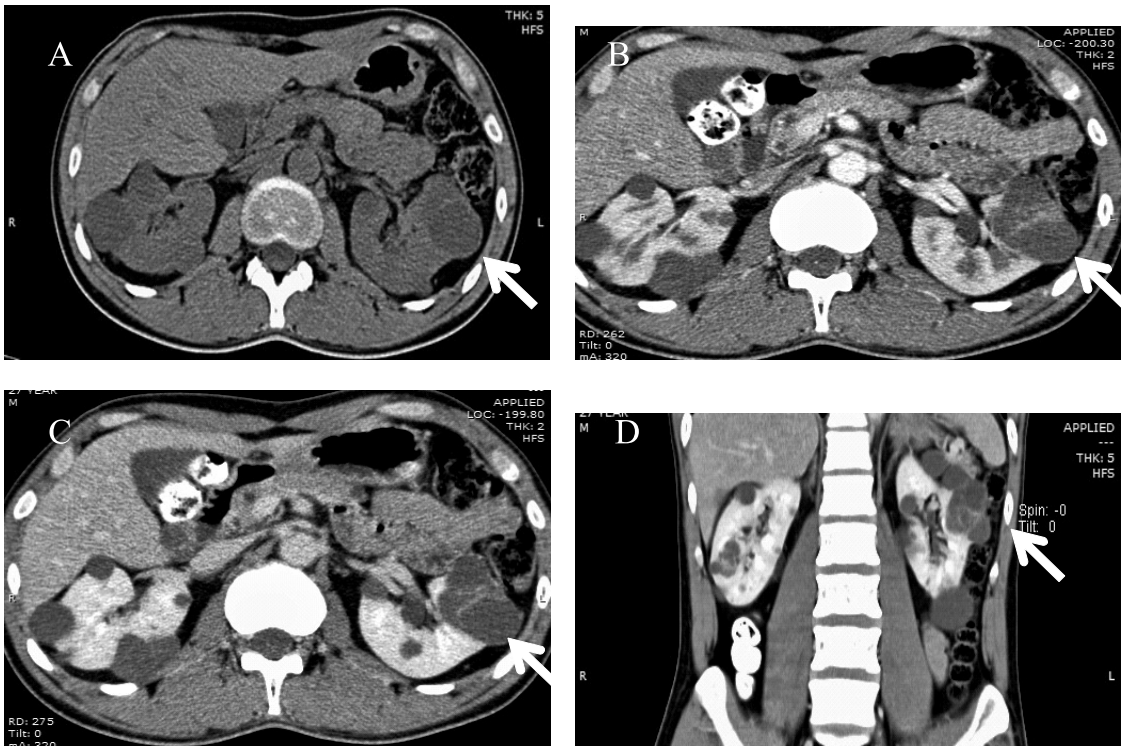

Figure 4. Images from a 27-year-old man with von Hippel–Lindau disease with multilocular cystic renal cell carcinoma. Axial and coronal precontrast (**A**), corticomedullary phase (**B**) and nephrogenic phase (**C** and **D**) images. **A**. Precontrast CT: A 2.5 cm × 3.0 cm multilocular cystic lesion at the midpole of the left kidney (arrow). **B**. Corticomedullary phase: enhancing thickened internal septa in the tumor. **C**. Nephrogenic phase: persist enhancement of thickened internal septa. **D**. The coronal image on nephrogenic phase: thickened enhance internal septa with multilocularity appearance of this tumor. He also had multiple simple renal cortical cysts in both kidneys, another multilocular cystic RCC in right kidney (arrowhead in D).

Discussion

In the present study, we evaluated preoperative CT characteristics of 38 histopathologically proven cystic RCCs. The incidence of cystic RCCs in patients at our tertiary care institution was 16%, which is slightly higher than found in other institutions, about 10% of all RCC [3]. There are 4 subtypes and mixed types of cystic RCCs. The most commonly found subtype was clear cell RCC, which consistent with previous studies. Our present findings show that solid enhancement was highest in clear cell RCC. Septal thickening, septal enhancement, and multilocularity are the important findings for differentiating subtypes of cystic RCCs, particularly between multilocular cystic RCC and other subtypes.

Pathological and radiological findings of cystic RCC were first described in 1986 by Hartman et al. [8]. There were 4 pathological findings of cystic RCC in that study: (1) intrinsic multiloculated growth, (2) intrinsic unilocular growth (cystadenocarcinoma), (3) cystic necrosis, and (4) origin from the epithelial lining of a preexisting simple cyst. The radiographic findings were classified into 3 patterns: (1) unilocular cystic mass (about 50% of cases), (2) multiloculated cystic mass (about 30% of cases), and (3) discrete mural nodule in a cystic mass (about 20% of cases).

Ool et al. [9] reviewed 11 cases of cystic RCC and first categorized 7 cases, which had preoperative CT, using criteria suggested by Bosniak. Like the present study, the study by Ool et al. found that all 7 cases were in Bosniak categories III and IV.

Cystic RCC has shown a lower nuclear grade, pathological stage, better prognosis, and longer 5-year survival than conventional solid RCC [4]. We propose that a conservative surgical approach should be the treatment of choice whenever technically feasible, because of the better prognosis of cystic RCCs. Overall and cancer-specific survival of patients with solid and cystic RCCs were prospectively compared by Huber et al. [6]. They found that patients with cystic RCCs showed significantly better overall and cancer-specific survival. Moreover, the present study found that median tumor diameter was smaller and nuclear grade of cystic RCC was more favorable than for solid RCCs.

Besides the morphology and radiology of cystic RCCs, histological subtype of the tumor is an important factor for predicting tumor aggressiveness and prognosis of patients. There is much recent literature describing the relationship of radiological findings and histopathological subtypes. Unilocular cystic RCC are usually of papillary or clear cell subtypes composed of a single cyst filled with serous or hemorrhagic fluid. The natural history of unilocular cystic masses is poorly understood because of their rarity, although they may metastasize [10, 11]. Cystic RCC with extensive tumor necrosis is usually of the clear cell type. Imaging findings of this subtype are irregularly thickened, and have enhancing septations and solid components. This subtype is the most aggressive form and may result in metastatic disease or death in up to 40% of cases [10]. Multilocular cystic RCC is a subtype of clear cell RCC, which is entirely composed of numerous cysts. Most common imaging findings of multilocular cystic masses are thick, enhancing septations surrounded by a well-defined fibrous capsule. Multilocular cystic RCC shows excellent prognosis with no known evidence of recurrence and metastasis. Nephron-sparing surgery is the treatment of choice for this subtype [11]. Histopathology is required to definitely differentiate multilocular RCC from cystic RCC because of necrosis. Multilocular cystic RCC should have tumor cell clusters less than 10% of the tumor volume and should not form gross nodules [10].

The most common histological subtype of RCC is clear cell RCC (about 70%) [12], which is consistent with our present findings. This tumor subtype has a worse prognosis when compared with chromophobe or papillary subtypes. However, nuclear grade and stage are also the accurate predictors of prognosis. Invasion of perirenal and sinus fat and/or extension into the renal vein occurs in about 45% of clear cell RCC [12]. Unique characteristics of clear cell cystic RCC in our present study were high contrast enhancement of the solid part or tumor, especially in the corticomedullary phase. This characteristic is similar to that of clear cell solid RCC. Clear cell RCCs have hypervascularity, because the pathogenesis of the tumor includes inactivation of the tumor suppressor gene (such as von Hippel–Lindau gene) and subsequently activation of vascular and growth factors [13]. Clear cell cystic RCCs mostly result from cystic change, necrosis, and hemorrhage of this tumor subtype. Therefore, solid attenuation of clear cell cystic RCCs may also help distinguish this subtype from nonclear cell cystic RCCs.

Another interesting finding were the CT characteristics of multilocular cystic RCC. We found that septal thickening, septal enhancement, and multilocularity were the distinctive findings of this subtype. However, this subtype is uncommon, accounting for about 2.3%-3.1% of all cases of RCC [7]. Only 4 multilocular cystic RCC lesions were found in our present study. Because of the limited cases of this subtype, this finding may be not be a certain predictor for this subtype's CT characteristics.

Our study has some limitations. First, it is retrospective. Second, we included a small group of patients and there was an inclusion bias. Only 1 chromophobe RCC lesion was found in our study, so our findings may not truly reflect findings for chromophobe RCCs. Third, because of the small number of patients, we did not calculate a precise cut-off value for contrast enhancement to predict tumor subtype. Fourth, various CT scanners and

section thicknesses were used, which may produce variability in some of the measurements. Finally, a subjective determination of internal heterogeneity of each lesion was used.

In conclusion, we found 4 subtypes and mixed types of cystic RCCs. Clear cell cystic RCCs were the most common subtype. A high degree of solid contrast enhancement was the distinctive finding for clear cell cystic RCC. Septal thickening, septal enhancement, and multilocularity are specific findings for multilocular cystic RCC. Preoperative CT findings may help clinicians and radiologists to predict tumor subtypes, because of different prognosis and treatment planning, particularly for multilocular cystic RCC.

Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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