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Differentiating renal cell carcinoma clear cell subtype from other subtypes on multiphasic multidetector computed tomography

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Background : *Renal cell carcinomas (RCC) represent about 1 - 3% of all visceral cancers and 85% of renal cancers in adults. The tumors occur most often in old age, usually in sixth and seventh decades of life, and more predominantly in males. There are different prognosis between each subtype of RCC and different targeted therapy of choice for clear cell and non-clear cell subtypes of RCC. Subtype differentiation of RCC is quite important for guided treatments and predicted prognosis. (according to the NCCN's Clinical Practice Guideline for Renal Cancer 2009).*

Objective : *This study aims to differentiate clear cell subtype of RCC from other subtypes on multiphase MDCT scans.*

Setting : *The Department of Radiology and Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.*

Research design : *Retrospective-Descriptive study*

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Material and Methods : *We reviewed CT scans of all RCC subtypes covering 33 clear-cell RCC, 12 papillary RCC and 4 chromophobe RCC. Nineteen CT scans, which consist of unenhanced, corticomedullary phase (CMP) and nephrographic phase (NP) scans and 28 CT scans (unenhanced, angiographic phase, CMP, NP and excretory phase scans) are included in the study. We compared tumor size, enhancement patterns, degree of tumor enhancement in these subtypes.*

Results : *Enhancement ratio in CMP and NP and absolute tumor enhancement in CMP are significantly different between clear -cell RCC and other RCCs ($P < 0.05$). We did not find any significance of absolute tumor enhancement in NP between clear- cell RCC and other RCCs. The sensitivity and specificity for differentiating clear- cell RCC from other RCCs were 75.8% and 75% when enhancement ratio of 0.45 was used as the cutoff value in the CMP and 75.8% and 62.5% when enhancement ratio of 0.43 was the cutoff value in the NP. The sensitivity and specificity for differentiating clear- cell RCC from other RCCs were 75.8% and 75% when absolute tumor enhancement of 48.8 HU was used as the cutoff value in CMP.*

Conclusions : *The enhancement ratio in CMP can be used for differentiating clear- cell RCC from other RCCs with equal sensitivity and specificity to absolute tumor enhancement in CMP. However, the area under the ROC curves of enhancement ratio is more than that of tumor absolute enhancement. Hence, the enhancement ratio could be superior to absolute tumor enhancement value for differentiating clear -cell RCC from other subtypes.*

Keywords : *Carcinoma, computed tomography, kidney, multiphasic, renal cell, enhancement ratio.*

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ณัฐพงศ์ เลิศลาภวศิน, เกวลี ศศิวิมลพันธุ์, วิภาวี กิตติโกวิท. การจำแนกมะเร็งไตชนิดย่อย Clear cell จากชนิดย่อยอื่น ๆ โดยการใช้ภาพเอ็กซเรย์คอมพิวเตอร์ multidetector โดยใช้เทคนิค multiphases. จุฬาลงกรณ์เวชสาร 2554 พ.ย. – ธ.ค.; 55(6): 543 – 58

เหตุผลของการทำวิจัย : *มะเร็งไตพบได้ประมาณร้อยละ 1 - 3 ของมะเร็งทั้งหมดที่เกิดกับอวัยวะภายในของร่างกาย และพบได้ประมาณร้อยละ 85 ของมะเร็งทั้งหมดที่เกิดกับไต มะเร็งไตส่วนมากพบในกลุ่มผู้ป่วยในช่วงอายุ 60 - 70 ปี และพบในผู้ป่วยเพศชายได้บ่อยกว่าเพศหญิง มะเร็งไตมีหลายชนิด มะเร็งไตชนิดย่อย clear cell มีการพยากรณ์โรคและการรักษาแบบเจาะจงเป้าหมาย (targeted therapy) ที่ต่างจากมะเร็งไตชนิดย่อยอื่น ๆ ดังนั้นหากเราสามารถจำแนกชนิดย่อยของมะเร็งไตทั้ง 2 กลุ่มออกจากจากกันได้จากภาพเอ็กซเรย์คอมพิวเตอร์อาจมีส่วนช่วยในการวางแผนการรักษาให้กับผู้ป่วยได้*

วัตถุประสงค์ : *หาความแตกต่างระหว่างมะเร็งไตทั้ง 2 ชนิดย่อยจากลักษณะภาพเอ็กซเรย์คอมพิวเตอร์ multidetector โดยใช้เทคนิค multiphases*

รูปแบบการวิจัย : *การศึกษาเชิงพรรณนาย้อนหลัง*

สถานที่ทำการศึกษา : *สาขารังสีวิทยาวินิจฉัย ภาควิชารังสีวิทยา และภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

ตัวอย่างและวิธีการศึกษา : *ทำการตรวจสอบภาพเอกซเรย์คอมพิวเตอร์ของผู้ป่วยมะเร็งไตชนิดย่อย Clear cell จำนวน 33 ราย ผู้ป่วยมะเร็งไตชนิดย่อย Papillary จำนวน 12 รายและผู้ป่วยมะเร็งไตชนิดย่อย Chromophobe จำนวน 4 ราย ภาพเอกซเรย์คอมพิวเตอร์ความเร็วสูงที่นำมาทำการศึกษาทั้งหมดจะต้องเป็นเทคนิคการตรวจแบบ multiphases ซึ่งอย่างน้อยจะต้องประกอบด้วย corticomedullary phase และ nephrographic phase โดยตัวแปรที่ทำการศึกษาในแง่ของขนาดของก้อนมะเร็ง, enhancement pattern, degree of enhancement*

ผลการศึกษา : *จากการศึกษาพบว่า enhancement ratio ในช่วง corticomedullary phaseและ nephrographic และค่า absolute tumor enhancement ในช่วง corticomedullary phase ของมะเร็งไตชนิดย่อย Clear cell แตกต่างจากมะเร็งไตชนิดย่อยอื่น ๆ อย่างมีนัยสำคัญทางสถิติ การจำแนกมะเร็งไตชนิดย่อยทั้งกลุ่มออกจากกันโดยใช้ค่า enhancement ratio (โดยใช้ค่า cut-off value ที่ 0.45) หรือ absolute tumor enhancement (โดยใช้ค่า cut-off value ที่ 48.8 HU) ในช่วง corticomedullary phase จะให้ความไวและความจำเพาะเท่ากันที่ร้อยละ 75.8 และ 75 ตามลำดับ หากเปลี่ยนมาใช้ค่า enhancement ratio ในช่วง nephrographic phase (โดยใช้ค่า cut-off value ที่ 0.43) จะมีความไวและความจำเพาะที่ร้อยละ 75.8 และ 62.5 ตามลำดับ*

สรุป : *เราสามารถจำแนกมะเร็งไตชนิดย่อย Clear cell ออกจากชนิดย่อยอื่น ๆ ได้โดยการใช้ค่า enhancement ratio ในช่วง corticomedullary phase และค่า absolute tumor enhancement ในช่วง corticomedullary phase ซึ่งทั้งสองค่าให้ความไวและความจำเพาะที่เท่ากัน อย่างไรก็ตาม ค่าพื้นที่ใต้กราฟของ ROC curve ที่ได้จาก enhancement ratio ในช่วง corticomedullary phase มากกว่าพื้นที่ใต้กราฟของ ROC curve ที่ได้จากค่า tumor absolute enhancement ดังนั้นในการจำแนกมะเร็งไตทั้ง 2 ชนิดย่อยออกจากกัน การใช้ค่า enhancement ratioในช่วง corticomedullary phase อาจดีกว่าการใช้ค่า absolute tumor enhancement*

คำสำคัญ : *มะเร็งไต, เครื่องเอ็กซเรย์คอมพิวเตอร์ชนิด multidetector, multiphases และ enhancement ratio.*

Renal cell carcinomas (RCC) represents about 1 - 3% of all visceral cancers and accounts for 85% of renal cancers in adult. According to WHO classification, there are three major subtypes of RCC, which include clear cell (conventional) RCC about 70 - 75%, papillary RCC about 10% and chromophobe RCC about 5%. The RCC subtype could be diagnosed by pathologic study and confirmed at the molecular level by cytogenetic and genetic analyses. [1-3] Each subtype of RCC has different prognosis. Among three major subtypes, clear- cell RCC carries worst prognosis and accounts for majority of cases that developed metastatic disease. However, response rate to systemic therapy for clear- cell subtype is higher than that of other subtypes.[2,3] Whereas papillary RCC has better prognosis than clear -cell RCC, chromophobe RCC has the best prognosis with 5-year disease-free survival rate up to 90%. [3-5]

Radical nephrectomy is recommended treatment for RCC.[1,6-7] Computed tomography (CT) with intravenous contrast material injection is considered the imaging modality of choice for the diagnosis and staging of RCC. Due to the recent development in technology, especially multidetector CT, it is now possible to obtain thinner slices with near isotropic data sets in very short period of time . [8] Cross -sectional imaging such as CT of the abdomen and pelvis, with and without contrast, and chest imaging are included in the initial workup and for treatment plan. [6] Moreover, CT scan can offer excellent anatomical details including assessment of renal vasculature, determining tumor vascularity and extension, providing advantage for selecting cases suitable for nephron-sparing surgery. [9 - 11] During the follow-up period, CT scan is also used as a tool for detection of local recurrence and distant metastases. [11]

Many studies attempted to use CT scan to differentiate RCC subtypes. [12-18] Recent studies suggested that degree of enhancement is the most useful parameter to differentiate subtypes of RCC. [15 - 17]

Methods

Subjects

The study was performed by searching hospital data base for cases with histological diagnosis of RCC based on ICD10 from January 1, 2003 to July 31, 2010. All cases must have definite pathological diagnosis of RCC. Thus, this study included 47 patients (34 men and 13 women) that have 49 tumors (33 clear- cell RCC, 12 papillary RCC and 4 chromophobe RCC).

Preoperative CT scan was performed using a multidetector CT scanner (Somatom Sensation plus 16; Siemens Medical Solution, Germany). As for upper abdomen studies, the scanning started at level of the dome of the right diaphragm to the lower pole of the kidneys, whereas for whole abdomen studies, the scan finished at level of symphysis pubis. All patients received bolus injection of 90 - 120 ml non-ionic monomer iodinate contrast material intravenously by power injector. Two CT techniques were used in this study: bolus tracking technique (bolus placed at the abdominal aorta at about T12/L1 level, triggered at 100 HU) about 19 cases (unenhanced, corticomedullary phase and nephrographic phase scans) and fixed delay time technique, with the delay time of approximately 30 seconds for angiographic phase, 60 seconds for corticomedullary phase and

90 seconds for nephrographic phase about 28 cases (unenhanced, angiographic phase, corticomedullary phase, nephrograhic phase and excretory phase scans) are included in the study.

Measures

All CT images were retrospectively reviewed by a 2-year experienced abdominal radiologist on picture archiving and communication systems (PACS). A radiologist was blinded to RCC subtypes. The tumor size was obtained by measuring the maximum diameter in the nephrographic phase by an electronic caliper in PACS.

Enhancement of target area was evaluated by determining the solid enhancing area. The region of interest (ROI) cursor was subsequently be placed on the area to measure for the attenuation value in each phase scan. The normal renal cortex in each phase scan in the same cut of the imaging was measured for enhancement ratio calculation. Calcification and cystic region was excluded from ROI cursor.

The degree of enhancement was evaluated by absolute tumor enhancement and enhancement ratio to the renal parenchyma.

Absolute tumor enhancement on corticomedullary phase (CMP) and nephrographic phase (NP) were calculated by the difference between tumor attenuation on plain scan study and post contrast studies i.e. CMP and NP, using the following equations[14]:

Absolute tumor enhancement in CMP = $Tumor_{CMP} - Tumor_{plain}$

Absolute tumor enhancement in NP = $Tumor_{NP} - Tumor_{plain}$

Where the TumorCMP, $Tumor_{NP}$ and $Tumor_{plain}$ represented tumor attenuation in CMP, NP and plain study, respectively.

Enhancement ratio would be obtained by using the following modified equations[14]:

Enhancement ratio in CMP = $[Tumor_{CMP} - Tumor_{plain}]/[Parenchyma_{CMP} - Parenchyma_{plain}]$

Enhancement ratio in NP = $[Tumor_{NP} - Tumor_{plain}]/[Parenchyma_{NP} - Parenchyma_{plain}]$

Where $Parenchyma_{CMP}$, $Parenchyma_{NP}$ and $Parenchyma_{plain}$ represented renal parenchymal attenuation in CMP, NP and plain study, respectively.

The enhancement pattern was described as homogeneous, heterogeneous or peripheral predominant (Fig 1a, 1b and 1c). The homogeneous enhancement pattern was assigned when almost all tumor area showed uniform enhancement. The tumor was considered predominate peripheral enhancement when most portion of tumor was not enhanced and only peripheral region showed enhancement. The remaining cases was classified as heterogeneous enhancement.

We also observed the tumor location, the presence of calcification or cystic degeneration, and the tumor spreading patterns (perinephric change, venous invasion, significant enlarged lymph node and distance metastasis). Perinephric change was indicated when there is evidence of strands of soft tissue attenuation in the perinephric area or thickening of Gerota's fascia (Fig. 2). Criteria for renal vein or IVC invasion include enhanced tumor thrombus within renal vein or IVC, nest of arterial tumor vessels extending into the renal vein or IVC, and linear striated capillary staining of tumor in the renal vein or IVC (Fig. 3a and 3b). A lymph node was considered significantly enlarged when it had short axis with the diameter of 1 cm or greater.

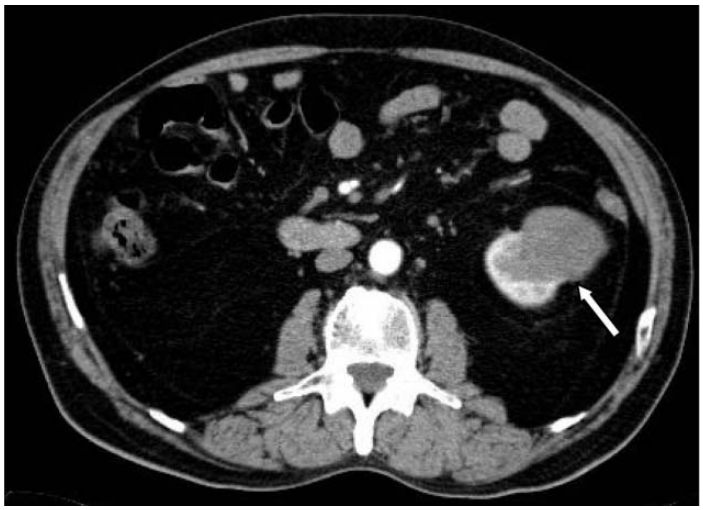

Figure 1a. A 74 year-old man with papillary RCC, Axial CT scan in corticomedullary phase shows a globular shape homogeneous enhancing mass at lower pole of left kidney.

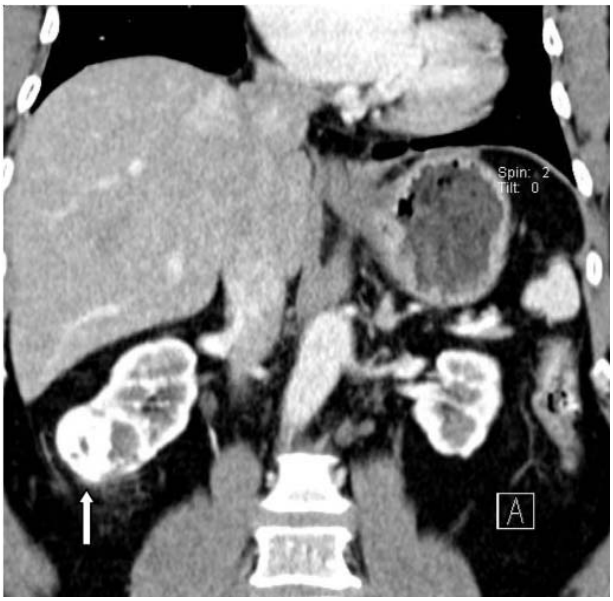

Figure 1b. A 57 year-old man with clear cell RCC, Coronal reformatted CT scan in corticomedullary phase shows an exophytic mass at lower pole of right kidney with heterogeneous enhancement pattern.

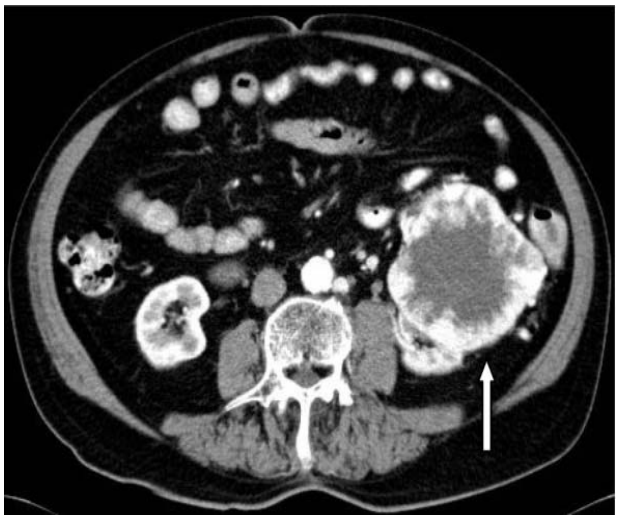

Figure 1c. A 86 year-old man with chromophobe RCC, Axial CT scan in corticomedullary phase shows a large lobulated mass at left kidney, displaying predominant peripheral enhancement.

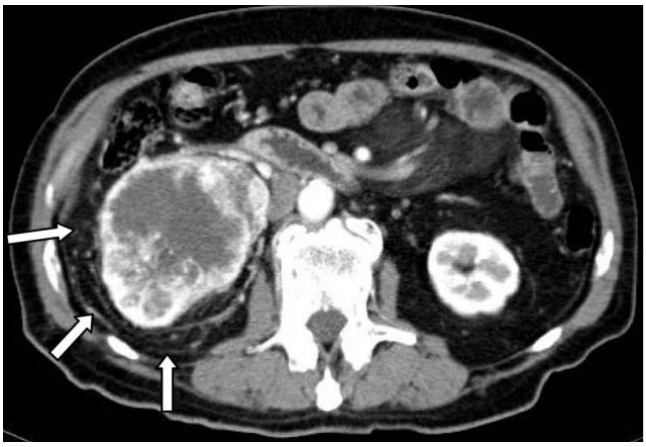

Figure 2. Axial CT scan in corticomedullary phase shows strands of soft tissue attenuation in right perinephric space.

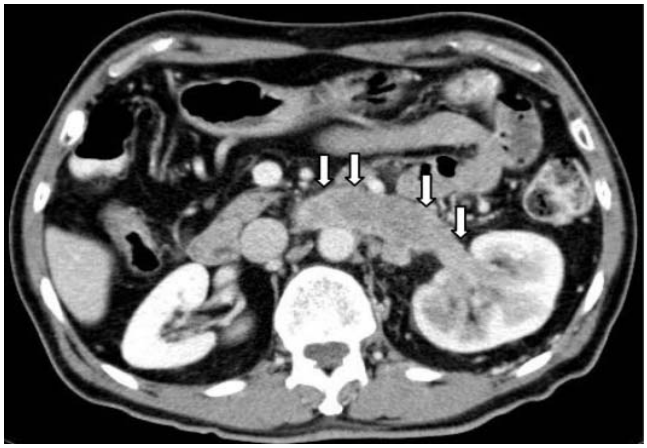

Figure 3a. Axial CT scan in nephrographic phase reveals filling defect in left renal vein and delayed nephrogram of left kidney.

Figure 3b. Coronal reformatted CT scan in nephrographic phase displays a tumor thrombus extending from left renal vein into IVC.

Tissue diagnosis was obtained from 47 patients, of whom 44 patients undergone radical nephrectomy; 1had received tumor enucleation; 1had metastatectomy (total hip replacement with tumor removal) and 1 had FNA (treated by Radiofrequency Ablation). Two patients were excluded from our study because of no definite pathologic subtype.

Statistical analysis

Statistical analysis was performed by using SPSS statistical analysis software for Window version 17.0 (IBM company). As for degree of tumor enhancement (either attenuation value or enhancement ratio), we used independent T-test for the analysis. To evaluate the diagnostic validity of the attenuation value and enhancement ratio in different subtype of RCC, ROC curves were generated and analyzed to determine the cutoff value for the differentiation with the highest accuracy. This study also describes the frequency found in the distribution of each subtype of RCC by age, sex, presence of calcification or cystic degeneration and tumor spreading pattern.

Results

The mean age and SD were 58 ± 11 years (range from 27 to 79) in patients with clear- cell RCC, 64 ± 12 years (range from 42 to 79) in patients with papillary RCC and 53 ± 14 (range from 40 to 69) in patients with chromophobe RCC (Table 2). The mean tumor diameter, mean tumor attenuation value in plain study, CMP and NP and mean enhancement ratio in CMP and NP were summarized in Table 1.

The male to female ratio was 3.6:1 for clear-cell RCC and 4.5:1 for papillary RCC. All patients with chromophobe RCC were female.

Calcification was found in 11 tumors (7 tumors with clear- cell RCC and 4 tumors with papillary RCC). Cystic degeneration was found in 12 tumors (8 tumors with clear- cell RCC, 2 tumors in papillary RCC and 2 tumors in chromophobe RCC).

Table 1. Mean ± SD of patient age, tumor size, attenuation and enhancement ratio in each phase of different RCC subtypes (mean ± SD).

	Clear cell RCC (n = 33)	**Papillary RCC (n = 12)**	**Chromophobe RCC (n = 4)**
Mean tumor diameter	6.96 ± 3.73	7.68 ± 5.62	11.10 ± 4.74
Cortex attenuation on plain scan	34.36 ± 4.81	33.47 ± 2.55	30.93 ± 5.27
Cortex attenuation on CMP	126.49 ± 40.97	141.58 ± 42.59	162.28 ± 8.70
Cortex attenuation on NP	147.06 ± 29.65	149.76 ± 26.47	191.60 ± 31.13
Tumor attenuation on plain scan	33.86 ± 6.52	36.58 ± 9.19	41.10 ± 9.10
Tumor attenuation on CMP	108.93 ± 39.47	68.79 ± 35.01	105.53 ± 34.59
Tumor attenuation on NP	99.46 ± 30.70	75.75 ± 23.28	106.28 ± 43.12
Enhancement ratio on CMP	0.93 ± 0.61	0.29 ± 0.23	0.52 ± 0.38
Enhancement ratio on NP	0.62 ± 0.33	0.35 ± 0.20	0.45 ± 0.31

The mean size of tumor with cystic degeneration was 11.1 ± 3.1 cm and the mean size of tumor without cystic degeneration was 6.3 ± 4.1 cm. We found that the mean sizes between clear cell and non-clear cell groups are statistically significant different ($P < 0.05$).

Renal vein or IVC invasion was found in 9 patients (6 clear- cell RCC, 2 papillary RCC and 1 chromophobe RCC). Perinephric change was found on imaging in 26 cases, but only 8 cases were pathologically positive. Sensitivity, specificity, PPV, NPV and accuracy of perinephric change on imaging were 100%, 50%, 30.8%, 100% and 59.1%, respectively. Significantly enlarged lymph nodes were noted on imaging of 4 cases, but none of these were positive on the pathologic study. Distance metastatic sites at the time of preoperative imaging were the lung (n = 6), the liver (n = 6) and bone (n = 1).

Data of gender, calcification, cystic degeneration, vascular invasion and spreading pattern were summarized in Table 2.

There was one tumor of papillary subtype with the background of chronic renal parenchymal disease. One subject in our study had VHL syndrome and multiple renal tumors, but only one tumor that had pathological proof was included in our study.

Independent T-test showed significant difference of enhancement ratio in CMP and NP and also absolute enhancement value of tumor in CMP between clear - cell RCC and non-clear cell RCCs (P = 0.001, 0.004 and 0.005, respectively). We did not find statistically significant difference in tumor absolute enhancement value in NP between clear-cell RCC and non-clear cell RCCs (P = 0.071).

The receiver operating characteristic (ROC) curves for enhancement ratio in CMP and NP and absolute enhancement value in CMP, in differentiating clear- cell RCC from non-clear cell RCCs were demonstrated in figure 4a, 4b and 4c. The area under the curve for enhancement ratio in CMP was 0.84 (95% CI 0.719 to 0.951) and its cutoff value with highest accuracy was 0.45. The area under the curve

Table 2. Frequency of sex, calcification, cystic degeneration and spreading patterns of different RCC subtypes.

	Clear cell RCC	**Papillary RCC**	**Chromophobe RCC**
Mean patient age	57.91 ± 11.36	63.83 ± 11.91	53.25 ± 13.60
- Male	56.73 ± 12.15	61.80 ± 11.85	-
- Female	62.29 ± 6.70	74.00 ± 7.07	53.25 ± 13.60
No. of male patient	25	9	0
No. of female patient	7	2	4
Calcification (n = 11)	7	4	0
Cystic degeneration (n = 12)	8	2	2
Venous invasion (n = 9)	6	2	1
Lung metastasis (n = 6)	4	1	1
Liver metastasis (n = 6)	5	0	1
Bone metastasis (n = 1)	0	1	0

for enhancement ratio in NP was 0.73 (95% CI 0.576 to 0.875) and its cutoff value with highest accuracy was 0.43. Figure 5 showed comparison between ROC curves obtained from enhancement ratio in CMP, enhancement ratio in NP and absolute enhancement value of tumor in CMP in differentiating clear cell subtype from other subtypes.

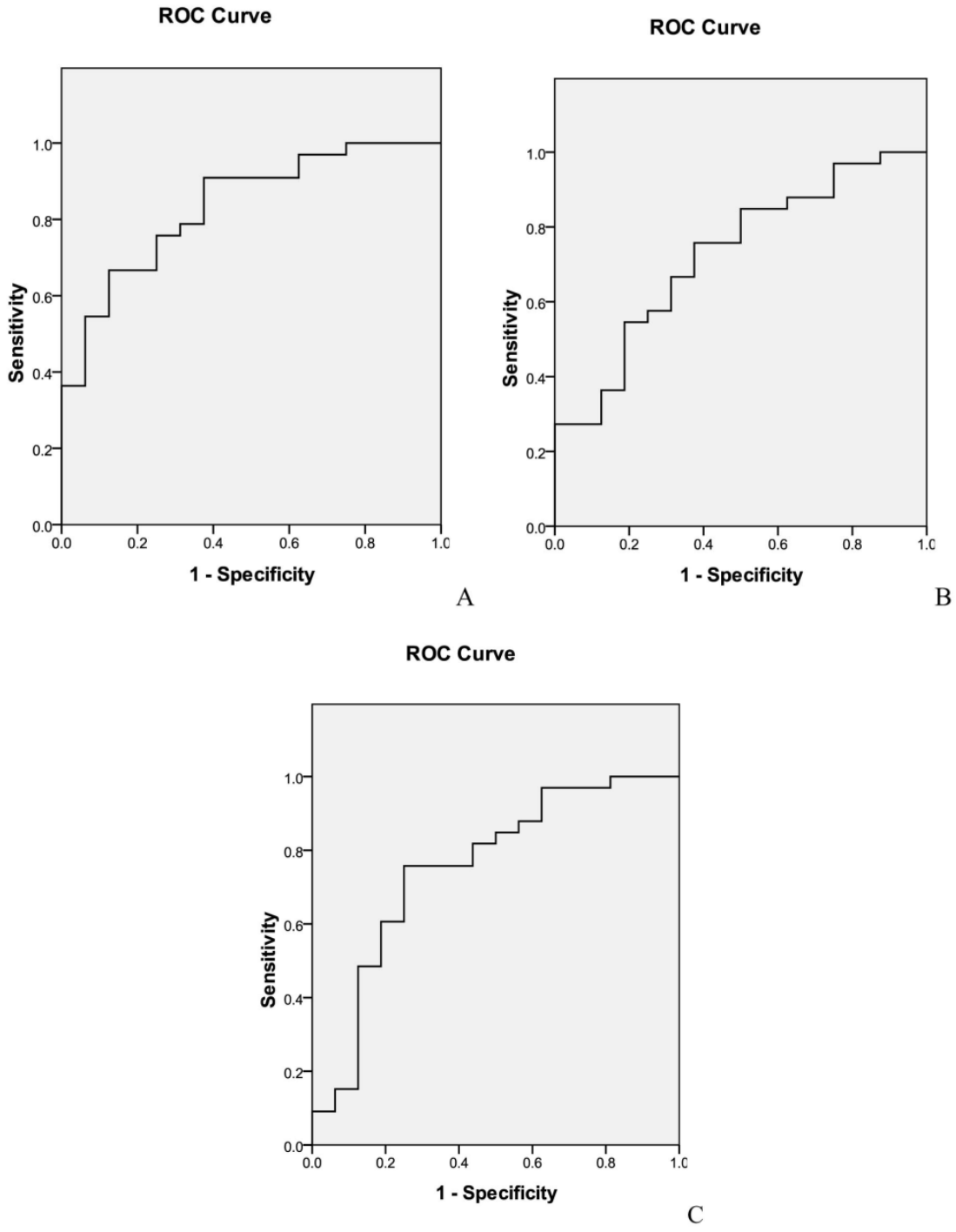

Figure 4. Receiver Operating Characteristics (ROC) curves to differentiate clear cell RCC from other RCCs of:
A, Enhancement ratio in CMP
B, Enhancement ratio in NP
C, Tumor absolute enhancement value in CMP

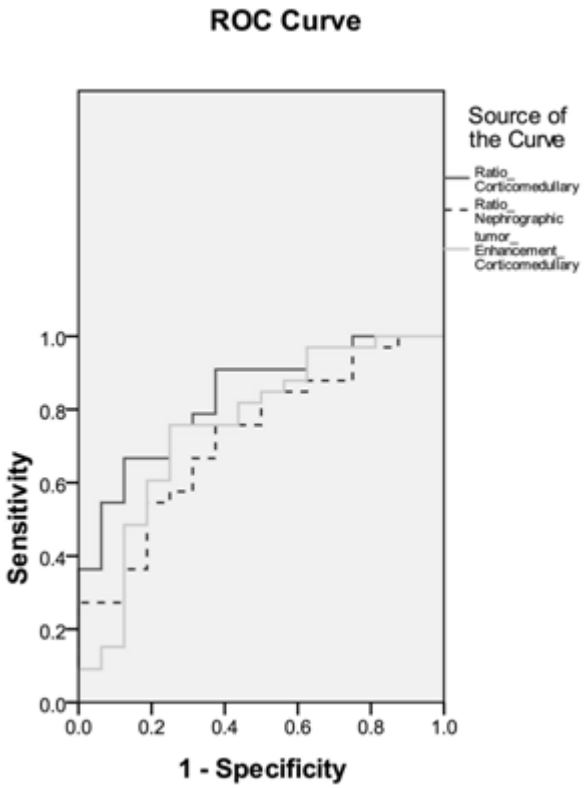

Figure 5. Comparison of ROC curves in figure 4a, 4b and 4c; ROC curves of the enhancement ratio in CMP has the most area under the curve of 0.84 (95% confident interval 0.719 - 0.951).

The area under the curve for absolute enhancement value in CMP was 0.75 (95% CI 0.598 to 0.909) and its cutoff value with highest accuracy was 48.8 HU.

From ROC analysis, we set criteria for differentiating clear cell from non-clear cell groups as follows:

1. Enhancement ratio in CMP $\geq$ 0.45
2. Enhancement ratio in NP $\geq$ 0.43
3. Absolute enhancement in CMP $\geq$ 48.8 HU

The sensitivity, specificity, PPV and NPV were showed in table 3, in case of 1 out of 3, 2 out of 3 and all three criteria above were reached.

Table 3. Sensitivity, Specificity, PPV and NPV of combined criteria.

Reached criteria	Sensitivity	Specificity	PPV	NPV
1 out of 3	87.87%	43.75%	76.3%	63.63%
2 out of 3	75.75%	75%	86.2%	60%
All three	63.63%	87.5%	91.3%	53.85%

Criteria for differentiating clear cell from non-clear cell

1. Enhancement ratio in CMP $\geq$ 0.45
2. Enhancement ratio in NP $\geq$ 0.43
3. Absolute enhancement in CMP $\geq$ 48.8 HU

Discussion

In 2004 WHO classified RCC into nine subtypes. There are three major subtypes of RCC, which include conventional (clear- cell) RCC (75%), papillary RCC (10%) and chromophobe RCC (5%). Factors influencing the prognosis are anatomical, histological, clinical, and molecular. The histologic factor includes Fuhrman grade, histological subtype, and presence of sarcomatoid features, microvascular invasion, tumor necrosis and also collecting system invasion. The RCC subtypes have been confirmed at the molecular level by cytogenetic and genetic analyses.[1 - 3] Different prognoses between each subtype of RCC have been well recognized. Accurate preoperative classifications of renal cell carcinoma subtypes may be beneficial for prognostic estimation and treatment planning.[3, 8 – 9]

As for patients who are not candidates for surgery, FNA is the alternative method to obtain a diagnosis. Unfortunately, up to 30% of renal FNA are non-diagnosted.[19] In patients with advanced stage disease, not suitable for nephrectomy and non-diagnostic FNA, imaging may help in decision making for the most appropriate targeted therapy.

In patient diagnosed with RCC, cross-sectional imaging such as MDCT of the abdomen and pelvis with and without contrast and chest imaging are essential studies in the initial workup and for treatment plan.

To our knowledge, there are several studies that attempted to differentiate subtypes of RCC by CT, For examples: Fujimoto *et al*. evaluated dynamic enhancement pattern of 96 RCC (with maximal tumor diameter of 5 cm) and reported that 72 cases have high attenuation on early enhanced scan (all of them are clear cell subtype with alveolar architecture).[12] Wildberger *et al*. observed several CT findings such as tumor nodule, shape and margin of tumor, pattern of fibrosis and enhancement patterns and found that the sensitivity for differentiating the clear- cell RCC from others, using their CT criteria, was approximately 72%[13], Brian R. Herts *et al*. analyzed 12 papillary RCC, 66 non-papillary RCC and 12 benign lesions and concluded that papillary RCC is more often hypovascular and homogeneous on CT than other RCCs with the tumor-to-aorta enhancement ratio or a tumor-to-kidney enhancement ratio of less than 0.25 suggests a higher degree of likelihood of papillary RCC.[14]

Recently, Kim *et al*. and Sheir *et al*. concluded that the degree of tumor enhancement is the most valuable parameter for differentiating RCC subtypes. In the study of Kim *et al*, the authors observed that the sensitivity and specificity for differentiating clear-cell RCC from other RCCs, using cutoff value of 84 HU in CMP, were 74% and 100%, respectively. At the cutoff value of 44 HU in excretory phase (EP), the sensitivity and specificity are 84% and 91%, respectively, while Sheir *et al* reported that 83.5 HU and 64.5 HU are the most accurate cutoff value for CMP and EP, respectively.[15-16] Dai *et al*. reviewed images of 460 RCC and found that clear- cell RCC showed stronger enhancement and more enhancement drop between corticomedullary phase and nephrographic phase, while chromophobe RCC showed middle level enhancement and papillary RCC was of little or no enhancement. At the cut off value of 30 HU for enhancement drop, clear- cell RCC could be differentiated from the other two subtypes.[17]

Early and strong enhancement of the clear - cell RCC is owing to its rich vascular fibrous stroma. [12, 20-21] Our study suggested that enhancement ratio in CMP can be used for differentiating clear-cell RCC from other RCCs with equal sensitivity and specificity to that of tumor absolute enhancement value. In the studies of Kim *et al* and Sheir *et al*, they attempted to use tumor absolute enhancement value for differentiating clear- cell RCC from others.

These two studies including ours have quite different cutoff values in tumor absolute enhancement value for differentiating clear- cell RCC from other RCCs. Based on ROC generated from the data in our study, we found that the cutoff value of 48.8 HU (too much from Kim = 84 and Sheir = 83.5) for tumor absolute enhancement in CMP is the most appropriate for differentiating clear -cell RCC from other RCCs. This cutoff value in our study is much different from that of Kim *et al* and Sheir *et al*, the result of which could be due to the difference in imaging protocol. Previous studies demonstrated that renal parenchymal and renal tumor enhancement depended on many factors, such as the volume of contrast material, time between injection and scanning of the contrast media, age of the patient. [22 - 23]

From our study sensitivity of 75.8% and specificity of 75% were obtained by using cutoff value of 48.8 HU in CMP. These values are lower than that of the studies of Kim *et al* with sensitivity of 74% and specificity of 100% and Sheir *et al* (no specific values given from this study). The lower sensitivity and specificity could be owing to smaller sample size or difference in imaging protocols.

Our study has found that enhancement drop between corticomedullary phase and nephrographic phase did not significantly differ, in contrast to the findings by the study of Dai *et al*. This could be owing to much smaller sample size in our study as compared to that of Dai *et al*., together with the difference on CT scan protocols.

Difference in the most appropriate cutoff values in each study could be explained by the facts that each patient has different hemodynamic status, and that each imaging center uses different scanner, imaging protocol and contrast material injection technique. As Kim *et al* mentioned in their study that their result could be applicable in only cases with similar injection protocol and scan time. We suggested that enhancement ratio, which uses renal parenchyma as internal reference, should be more applicable than the use of tumor absolute enhancement value. Moreover, ROC analysis from our study shows that the AUC of enhancement ratio in CMP is more than the AUC of tumor absolute enhancement value (0.84 *vs* 0.75), confirming our suggestion. However, the most appropriate cutoff values of enhancement ratio in CMP and absolute enhancement value in CMP give the same sensitivity and sensitivity. Hence, further investigation is needed to clarify superiority of enhancement ratio over absolute enhancement value.

Conclusion

Our study confirmed that there is difference enhancement pattern between clear- cell RCC and other subtypes. Degree of enhancement, either in the context of enhancement ratio or absolute

enhancement value in CMP, is the most effective parameter for differentiating clear- cell RCC from other subtypes. The enhancement ratio in CMP could have superiority to absolute enhancement value CMP but further investigation is needed.

References

1. Ljungberg B, Hanbury DC, Kuczyk MA, Merseburger AS, Mulders PF, Patard JJ, Sinescu IC. Renal cell carcinoma guideline. Eur Urol 2007 Jun; 51(6):1502-10
2. Lopez-Beltran A, Scarpelli M, Montironi R, Kirkali Z. 2004 WHO classification of the renal tumors of the adults. Eur Urol 2006 May; 49(5): 798-805
3. Prasad SR, Humphrey PA, Catena JR, Narra VR, Srigley JR, Cortez AD, Dalrymple NC, Chintapalli KN. Common and uncommon histologic subtypes of renal cell carcinoma: imaging spectrum with pathologic correlation. Radiographics 2006 Nov; 26(6): 1795-806
4. Reuter VE. The pathology of renal epithelial neoplasms. Semin Oncol 2006 Oct; 33(5): 534-43
5. Crotty TB, Farrow GM, Lieber MM. Chromophobe cell renal carcinoma: clinicopathological features of 50 cases. J Urol 1995 Sep;154(3): 964-7
6. Motzer RJ, Agarwal N, Beard C, Bolger GB, Boston B, Carducci MA, Choueiri TK, Figlin RA, Fishman M, Hancock SL, et al. NCCN clinical practice guidelines in oncology: kidney cancer. J Natl Compr Canc Netw 2009 Jun; 7(6): 618-30
7. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet 2009 Mar; 373(9669): 1119-32
8. Israel GM, Bosniak MA. Renal imaging for diagnosis and staging of renal cell carcinoma. Urol Clin North Am 2003 Aug; 30(3): 499-514
9. Sheth S, Scatarige JC, Horton KM, Corl FM, Fishman EK. Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector ct and three-dimensional CT. Radiographics 2001 Oct; 21 Spec No: S237-54
10. Ghersin E, Amendola MA, Engel A. Computed tomography in renal cell carcinoma. In: Hayat MA, ed. Cancer Imaging. London: Elsevier Academic Press, 2008: 445-55
11. Bach AM, Zhang J. Contemporary radiologic imaging of renal cortical tumors. Urol Clin North Am 2008 Nov; 35(4): 593-604
12. Fujimoto H, Wakao F, Moriyama N, Tobisu K, Sakamoto M, Kakizoe T. Alveolar architecture of clear cell renal carcinomas (< or = 5.0 cm) show high attenuation on dynamic CT scanning. Jpn J Clin Oncol 1999 Apr; 29(4): 198-203
13. Wildberger JE, Adam G, Boeckmann W, Munchau A, Brauers A, Gunther RW, Fuzesi L. Computed tomography characterization of renal cell tumors in correlation with histopathology. Invest Radiol 1997 Oct; 32(10): 596-601
14. Herts BR, Coll DM, Novick AC, Obuchowski N, Linnell G, Wirth SL, Baker ME. Enhancement characteristics of papillary renal neoplasms revealed on triphasic helical CT of the kidneys. AJR Am J Roentgenol 2002 Feb; 178(2):

367-72

15. Kim JK, Kim TK, Ahn HJ, Kim CS, Kim KR, Cho KS. Differentiation of subtypes of renal cell carcinoma on helical CT scans. AJR Am J Roentgenol 2002 Jun; 178(6): 1499-506
16. Sheir KZ, El Azab M, Mosbah A, El Baz M, Shaaban AA. Differentiation of renal cell carcinoma subtypes by multislice computerized tomography. J Urol 2005 Aug; 174(2): 451-5
17. Dai JR, Zhang LY, Zhang J, Chen Y, Zhang HT, Jiang LX, Lin M. Differentiation of subtypes of renal cell carcinoma by double-phase helical computed tomography. Zhonghua Yi Xue Za Zhi 2010 Aug; 90(31): 2177-81
18. Yamada T, Endo M, Tsuboi M, Matsuhashi T, Takase K, Higano S, Takahashi S. Differentiation of pathologic subtypes of papillary renal cell carcinoma on CT. AJR Am J Roentgenol 2008 Nov; 191(5): 1559-63
19. Renshaw AA, Cibas ES. Kidney and adrenal gland. In: Cibas ES, Ducatman BS, eds. Cytology: Diagnostic Principles and Clinical Correlates. 3rd ed. Philadelphia: Saunders, 2009: 403-32
20. Oyen R, Van Poppel H, Roskams T. Primary malignant renal parenchymal epithelial neoplasms in adults. In: Gourtsoyiannis NC, Ros PR, eds. Radiologic-Pathologic Correlations from Head to Toe: Understanding the Manifestations of Disease. Berlin: Springer, 2005: 596-616
21. Grignon DJ, Eble JN, Bonsib SM, Moch H. Clear cell renal cell carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon: IARC Press, 2004: 23-25
22. Birnbaum BA, Jacobs JE, Ramchandani P. Multiphasic renal CT: comparison of renal mass enhancement during the corticomedullary and nephrographic phases. Radiology 1996 Sep; 200(3): 753-8
23. Birnbaum BA, Jacobs JE, Langlotz CP, Ramchandani P. Assessment of a bolus-tracking technique in helical renal CT to optimize nephrographic phase imaging. Radiology 1999 Apr; 211(1): 87-94