

# Evaluation of the Relative Enhancement Ratio and Morphologic Findings on Biphasic CT to Differentiate Clear Cell and Non-Clear Cell Renal Cell Carcinoma

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## ABSTRACT

**Objective:** To differentiate clear cell and non-clear cell renal cell carcinoma (RCC) using enhancement pattern, relative enhancement ratio and associated findings on CT scan.

**Methods:** This retrospective study reviewed CT scan in the unenhanced, corticomedullary and nephrographic phase in clear cell and non-clear cell RCC. A total of 49 patients with surgically proven RCC, consisting of 42 clear cell RCCs, and 7 non-clear cell RCCs (6 papillary, 1 chromophobe). Two radiologists compared degree of enhancement, enhancement pattern, the presence or absence of calcification, perinephric change, pelvocalyceal involvement, neovascularization, venous invasion, lymphadenopathy and distant metastasis.

**Results:** Both the attenuation value and degree of enhancement in the corticomedullary phase were higher in clear cell RCC than non-clear cell RCC. The relative enhancement ratio in the corticomedullary phase was significantly higher in clear cell than non-clear cell RCC. The cutoff value of the relative enhancement ratio higher than 1.629 was used to differentiate clear cell RCC from non-clear cell RCC and had the sensitivity, specificity, PPV, NPV and accuracy of 76.2%, 85.7%, 97%, 37.5% and 77.6%, respectively. Heterogeneous enhancement, perinephric change and neovascularization were found significantly more common in clear cell than non-clear cell RCC.

**Conclusion:** The most useful parameter to differentiate clear cell from non-clear cell RCC is relative enhancement ratio in the corticomedullary phase.

**Keywords:** Biphasic CT, clear cell renal cell carcinoma, non-clear cell renal cell carcinoma

**Abbreviations:** Computed tomography (CT), renal cell carcinoma (RCC)

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## INTRODUCTION

**R**enal cell carcinoma (RCC) is the most common type of renal cancer in adults and is the 13<sup>th</sup> most common malignancy world

wide<sup>1</sup>. Male is more predominant than female about 1.5 times<sup>2</sup>. Continued increase in the incidence of RCC globally has been noted, partly due to early diagnosis with cross-sectional imaging modalities<sup>3</sup>.

Histologic subtypes according to the 2004 World Health Organization (WHO) classification include clear cell RCC (70%), papillary RCC (10%), chromophobe RCC (5%), hereditary cancer syndromes (5%), multilocular cystic RCC (<1%), collecting duct carcinoma (<1%), medullary

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carcinoma (<1%), mucinous tubular and spindle cell carcinoma (<1%), neuroblastoma-associated RCC (<1%), Xp11.2 translocation-TFE3 carcinoma (<1%), and unclassified lesions (4-5%)<sup>4,5</sup>. The distinct histomorphologic subtype has an influence on the prognosis. The metastatic potential of RCC shows that the aggression seems to be greater in the clear cell subtype (65%), decreases in the papillary (14%; intermediary risk), and is least in the chromophobe RCC (8%; lower risk)<sup>6</sup>. Accurate histologic and imaging characterization of RCC is very important for prognostic prediction and appropriate extent of surgical planning.

In our study, we compared contrast-enhanced CT findings in clear cell and non-clear cell RCC and analyzed which CT features would be helpful in differentiating among these groups.

## MATERIALS AND METHODS

### Patients

A retrospective study was approved by the Ethics Committee (Si. 275/2011). A computer search of pathologic and surgical records obtained in Siriraj Hospital during a 5-year period (from January 2006 - February 2011) discovered 323 patients with a pathologically proven RCC. The patients were excluded if there were no images in picture archiving and communication system (PACS) or non-complete biphasic CT scan of kidneys (corticomedullary and nephrographic phases). Therefore, of these 323 patients, 274 patients were excluded from the study. Finally, we received 49 patients, 19 males and 30 females, aged 17-84 years. These surgically proven RCC in 49 patients were comprised of 42 clear cell, 6 papillary, and 1 chromophobe subtypes.

### CT technique

All CT examinations were performed using 64 slice CT scanners; Dual source CT (Siemens) and LightSpeed VCT (GE). CT scans were obtained with the following parameters for imaging acquisition and reconstruction: 120 kVp; 500 mA; section collimation, 5 mm; table feed, 7 mm/sec; and reconstruction interval 1, 7 mm. All patients received about 100 ml of intravenous non-ionic contrast medium administration.

All examinations included unenhanced, corticomedullary phase (delayed 30 seconds after IV contrast medium injection) and nephrographic phase (delayed 100-120 seconds after IV contrast medium injection). Scanning area included the entire kidneys.

### Image analysis

All image interpretations were made by two genitourinary radiologists who were blinded to the pathologic subtype of RCC. Radiologists evaluated tumor characterization: degree and pattern of enhancement, calcification, perinephric change, pelvocalyceal involvement, neovascularization, venous invasion, lymphadenopathy and distant metastasis. Any discordant results were resolved by consensus.

Degree of enhancement was done by measuring attenuation of three separate regions of interest in the tumor. A round region-of-interest was at least 1 cm<sup>2</sup> and placed over the solid enhancing portion of the tumor. The measurements were performed in all unenhanced, corticomedullary and nephrographic phases in the same region. We calculated the mean of these three values. Then the average attenuation of each RCC subtype was calculated.

The relative enhancement ratio in the corticomedullary and nephrographic phases were calculated for more comparable degree of enhancement in each case as follows:

$$\frac{[\text{Average attenuation in corticomedullary phase} - \text{Average attenuation in unenhanced phase}]}{[\text{Average attenuation in unenhanced phase}]}$$

$$\frac{[\text{Average attenuation in nephrographic phase} - \text{Average attenuation in unenhanced phase}]}{[\text{Average attenuation in unenhanced phase}]}$$

$$\frac{[\text{Average attenuation in nephrographic phase} - \text{Average attenuation in unenhanced phase}]}{[\text{Average attenuation in unenhanced phase}]}$$

The enhancement pattern of tumor was classified in two patterns including homogeneous and heterogeneous enhancement.

Perinephric change was determined by demonstrable perinephric soft tissue stranding or perinephric nodule.

Neovascularization was indicated when there were new blood vessel formations in the tumor.

Renal vein or inferior vena cava invasion was determined by a low attenuation filling defect within the lumen.

Lymphadenopathy was determined by nodal enlargement of greater than 1 cm in short axis.

### Statistical analysis

Renal cell carcinoma (RCC) was classified into two groups including clear cell and non-clear cell RCC. The CT findings of these two groups were compared statistically. All quantitative data, including age of patients and attenuation of the lesion were described by mean and average. Chi-square test or Fisher's exact test was used to analyze radiographic findings; frequency of each enhancement pattern, the presence or absence of calcification, perinephric change, pelvocalyceal system involvement, the presence or absence of neovascularization, venous invasion, lymphadenopathy and distant metastasis. The *p*-value was also used and considered to be significant if less than 0.05. Receiver operating characteristic curves (ROC) were generated and analyzed to determine the cutoff of the relative enhancement ratio in differentiating subtypes of RCC.

## RESULTS

A total of 49 patients were diagnosed with 42 clear cell RCC, 7 non-clear cell RCC (6 papillary subtypes, 1 chromophobe subtype). The mean patient age of clear cell RCC, papillary RCC and chromophobe RCC were 61.47 years, 49 years, and 38 years respectively. The mean patient age for all subtypes was 59.46 years (range 17-84 years). Of 49 patients, there were 19 males (16 clear cell, 3 papillary subtypes) and 30 females (26 clear cell, 3 papillary, 1 chromophobe subtypes).

### *The average attenuation and degree of enhancement*

The average attenuation and the degree of enhancement were summarized in Table 1. In the corticomedullary phase, both the average attenu-

ation and degree of enhancement were higher in clear cell RCC than in all subtypes of non-clear cell RCC. The average attenuation and degree of enhancement in the corticomedullary phase were higher than the nephrographic phase in clear cell RCC (Fig 1).

In the nephrographic phase, both the average attenuation and degree of enhancement were higher in clear cell RCC than in 5 of the 6 cases of papillary subtype and one chromophobe subtype. However, there was one case of papillary subtype that the average attenuation and degree of enhancement in the nephrographic phase were slightly higher than clear cell RCC (Fig 2).

### *The relative enhancement ratio*

The relative enhancement ratio in the corticomedullary and nephrographic phases showed significant difference between clear cell RCC and non-clear cell RCC ( $p=0.004$  and  $p=0.024$  respectively). The receiver operating characteristic curve (ROC) for the relative enhancement ratio in the corticomedullary and nephrographic phases for differentiation of clear cell RCC from non-clear cell RCC were demonstrated in Fig 3.

For the corticomedullary phase, the area under the curve (Az value) was 0.84 (95% confidence interval [CI]: 0.701-0.979). The cutoff value of the relative enhancement ratio in the corticomedullary phase with the highest accuracy for the differentiation of clear cell RCC from non-clear cell RCC was more than 1.629 with the sensitivity, specificity, PPV, NPV and accuracy at 76.2%, 85.7%, 97%, 37.5% and 77.6% respectively.

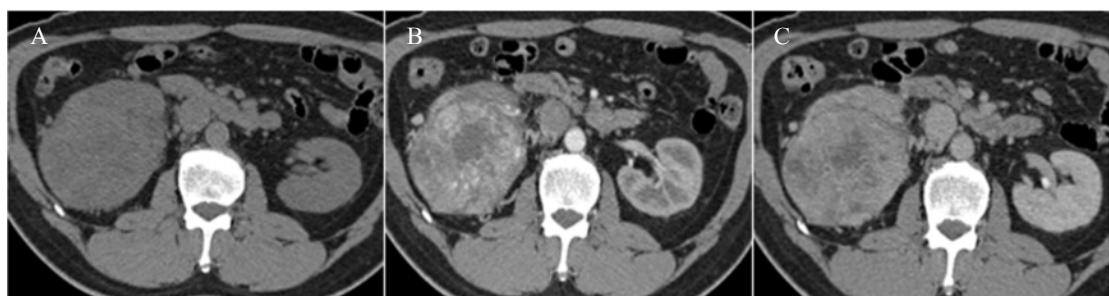
For the nephrographic phase, the area under the curve (Az value) was 0.759 (95% confidence interval [CI]: 0.615-0.869). The cutoff value of the relative enhancement ratio in the nephrographic phase with the highest accuracy for the differentiation of clear cell RCC from non-clear cell RCC was more than 1.439 with the sensitivity, specificity, PPV, NPV and accuracy at 76.2%, 71.4%, 91.4%, 28.6% and 73.5% respectively.

### *Enhancement pattern*

Heterogeneous enhancement was found mostly in both clear cell RCC (100%) and non-clear cell RCC (85.7%). Frequency of heterogeneous

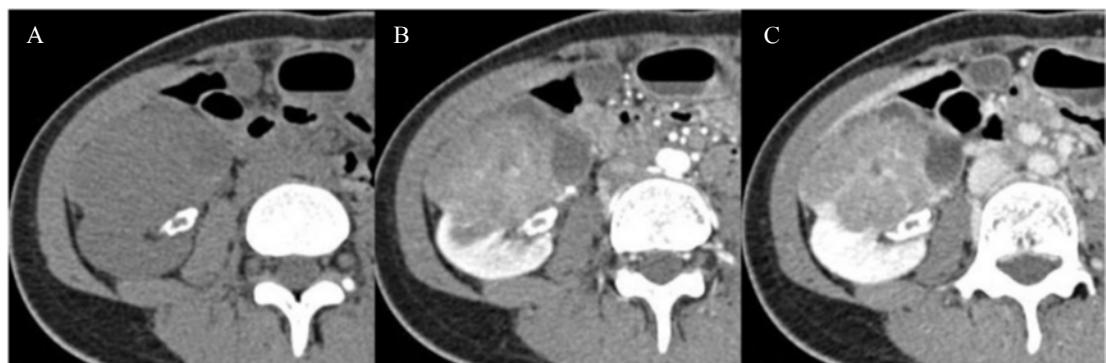
**TABLE 1.** Average attenuation and degree of contrast enhancement of four RCC subtypes.

CT Phase	Average attenuation and degree of contrast enhancement of RCC subtypes (HU)		
	Clear cell (n=42)	Papillary (n=6)	Chromophobe (n=1)
Unenhanced phase			
Attenuation	33.0	35.7	34.3
Corticomedullary phase			
Attenuation	114.9	70.0	50.7
Enhancement	81.9	34.3	16.4
Nephrographic phase			
Attenuation	100.9	76.9	59.3
Enhancement	67.9	41.2	25.0



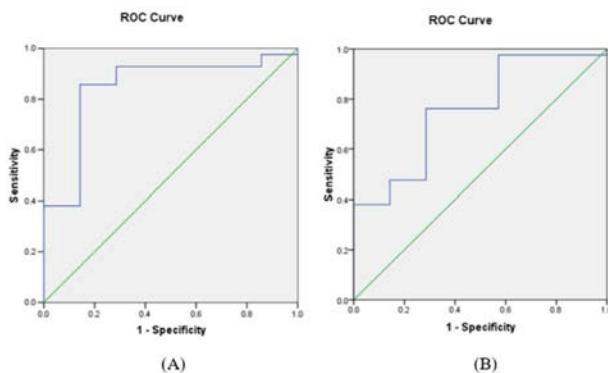
**Fig 1.** A 56-year-old man with clear cell RCC.

A. Unenhanced CT scan showed an exophytic mass at right kidney.  
B. Corticomedullary phase and C. nephrographic phase showed heterogeneous enhancement pattern of this mass and predominant enhancement in corticomedullary phase.



**Fig 2.** A 17-year-old woman with papillary RCC.

A. Unenhanced CT scan showed an exophytic mass at right kidney (attenuation value was 31.7 HU). A right renal stone was noted.  
B. This mass showed heterogeneous enhancement in corticomedullary phase (attenuation value was 82.8 HU).  
C. Increase in degree of enhancement of this mass in nephrographic phase was noted (attenuation value was 107.5 HU).



**Fig 3.** The receiver operating characteristic curve for relative enhancement ratio in differentiation of clear cell RCC from non-clear cell RCC

A. In corticomedullary phase, area under curve (Az value) was 0.84 (95% confidence interval [CI]: 0.701-0.979).  
 B. In nephrographic phase, area under the curve (Az value) was 0.759 (95% confidence interval [CI]: 0.615-0.869).

enhancement was higher in clear cell RCC (Fig 1) with statistical significance ( $p=0.013$ ).

Homogeneous enhancement was found in only one case of non-clear cell RCC which was chromophobe RCC (Fig 4).

#### Associated findings

All data about associated findings were shown in Table 2.

## DISCUSSION

Each subtype of renal cell carcinoma (RCC) is associated with a different prognosis and tumor behavior. Clear cell RCC has a less favorable prognosis than do papillary RCC and chromophobe RCC<sup>5</sup>.



**Fig 4.** A 38-year-old woman with chromophobe RCC.

A. Unenhanced CT scan showed an exophytic mass at left kidney.  
 B. Corticomedullary phase and C. nephrographic phase revealed homogeneous enhancement pattern of this mass.

**TABLE 2.** Associated findings between clear cell RCC and non-clear cell RCC.

Associated findings	Clear cell RCC (n=42)	Non-clear cell RCC (n=7)	P value
Calcification	27 (64.3 %)	4 (57.1%)	0.717
Perinephric change	40 (95.2%)	4 (57.1%)	0.002
Pelvocalyceal involvement	25 (59.5%)	3 (42.9%)	0.409
Neovascularization	31 (73.8%)	1 (14.3%)	0.002
Venous invasion	17 (40.5%)	2 (28.6%)	0.550
Lymphadenopathy	13 (31.0%)	3 (42.9%)	0.534
Liver metastasis	4 (9.5%)	1 (14.3%)	0.700
Lung metastasis	10 (23.8%)	0	0.148
Adrenal metastasis	4 (9.5%)	2 (28.6%)	0.155
Bone metastasis	1 (2.4%)	0	0.680

Kim et al,<sup>7</sup> found that clear cell RCC showed stronger enhancement than non-clear cell RCC in both the corticomedullary and excretory phases, and the tumors that enhanced more than approximately 84 HU in the corticomedullary phase and 44 HU in the excretory phase were likely to be clear cell RCC. Fujimoto et al,<sup>8</sup> reported that strong enhancement equal to the renal cortex was noted only in clear cell RCC (75%) and not in the other subtypes of RCC.

Our study found that clear cell RCC showed stronger enhancement than chromophobe RCC and also in 5 of the 6 cases of papillary RCC in both the corticomedullary and nephrographic phases. However, there was one case of papillary subtype that the average attenuation and degree of enhancement in the nephrographic phase were slightly more than clear cell RCC.

The average attenuation and degree of enhancement in the corticomedullary phase were higher than the nephrographic phase in clear cell RCC. One chromophobe RCC and 5 cases of papillary RCC in the nephrographic phase, showed slightly increased attenuation compared to the corticomedullary phase, but not a significant enhancement. For one case of papillary RCC, there was a significant increase in degree of enhancement in the nephrographic phase compared to the corticomedullary phase.

The relative enhancement ratio in the corticomedullary and nephrographic phases were calculated by using the difference of average attenuation of both phases and average attenuation of unenhanced phase divided by average attenuation of unenhanced phase. After using the ROC curve to determine cutoff value for differentiating the RCC, this study found stronger enhancement in the corticomedullary phase of clear cell RCC than the non-clear cell RCC ( $p = 0.004$ ) with good validity ( $Az$  value = 0.84) corresponding with a prior study of Kim et al.<sup>7</sup> A cutoff value of the relative enhancement ratio more than 1.629 revealed highest sensitivity, specificity, PPV, NPV and accuracy (76.2%, 85.7%, 97%, 37.5% and 77.6% respectively) to predict possibility of clear cell RCC. For the nephrographic phase, the area under the ROC curve ( $Az$  value) was 0.759 (95% confidence interval [CI]: 0.615–0.869) which was fair validity

compared to the good validity of the corticomedullary phase. However, the cutoff value at more than 1.439 could be helpful for differentiating clear cell RCC from non-clear cell RCC.

The enhancement pattern (heterogeneous enhancement), the presence of neovascularization and perinephric change were the only three findings which may be helpful to distinguish clear cell from non-clear cell RCC with statistical significance ( $p < 0.05$ ). However, perinephric change was also found in four cases of non-clear cell RCC. Besides, the stage and size of each tumor were not included in the analysis which could influence the presence of neovascularization and perinephric change. It might be necessary for further studies to prove these results.

The presence or absence of calcification, pelvocalyceal system involvement, venous invasion and lymphadenopathy coincided in both clear cell and non-clear cell RCC with no statistically significant difference ( $p > 0.05$ ).

In clear cell RCC, our study showed the most frequent metastatic organs were lung (23.8% of all cases), followed by liver (9.5%), adrenal glands (9.5%) and bone metastasis (2.4%). Two cases of papillary RCC had adrenal metastasis and one case of papillary RCC had liver metastasis. However, there was no demonstrable statistically significant difference between clear cell and non-clear cell RCCs, which could be a consequence of small sample size.

Due to insufficient sample size of each subtype of non-clear cell RCC patients in this study, it caused an inability to analyze CT findings in each subtype. However, the study showed homogeneous enhancement in chromophobe RCC ( $n=1$ ), corresponding to a prior report<sup>7</sup>.

The female populations in this study were higher than male (female 61.2% and male 38.8%) which was different from prior demographic data<sup>2</sup>, possibly due to small sample size.

There were some limitations in this study because of a small number of total patients. Besides, there were limited cases of non-clear cell RCC, resulting in an inability to analyze CT features. Finally, due to retrospective study design which caused different image scan time and amount of contrast medium administration param-

eters resulting in non-uniform protocol setting in each CT examination. These varied parameters could affect enhancement value measurement.

## CONCLUSION

The most useful parameter in this study to differentiate clear cell from non-clear cell RCC was relative enhancement ratio in corticomedullary phase with high sensitivity, specificity, PPV, NPV and accuracy. This study also found significant enhancement in corticomedullary phase in clear cell RCC.

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