RADIOLOGIC CHARACTERISTICS OF COMPUTERIZED TOMOGRAPHY ATTENUATION IN RENAL CELL CARCINOMA

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Background: Renal cell carcinoma (RCC) is the most common kidney cancer in adults. Computed Tomography (CT) with contrast study is used to diagnose RCC. The enhancement in the nephrogenic phase more than 15 Hounsfield units (HU) is suspected of RCCs. However, this threshold HU shows 15-20% false positive results for RCCs.
Objectives: This study aimed to determine RCC enhancement in CT that was below the standard threshold and to analyze the attenuation range of RCCs in noncontrast CT.
Methods: Patients with pathological RCC and undergoing CT with contrast study were retrospectively reviewed. An average of attenuation values of three regions of interest (ROI) were measured in noncontrast and nephrogenic phases, by avoiding foci of calcification and peritumoral region. ROI values were calculated for enhancement and range of attenuation values in the noncontrast CT.
Results: A total of 152 pathologically RCCs were included in the study. Mean ± SD attenuation values were 32.54 ± 8.02 HU (range 13.3-57.23 HU) and 71.26 ± 33.1 HU (range 16.87-202.8 HU) for noncontrast and contrast CT, respectively. Thirty-one (20.4%) of RCCs did not reach 15 HU enhancement. Using multivariate analysis, significant differences among subtypes (p<0.001) and renal mass less than 7 cm (p<0.001) were observed. In noncontrast CT, using a range of 20-60 HU, 129 (84.9%) RCCs were entirely within this range. To improve the accuracy of RCC diagnosis, the combined use of both non-contrast attenuation group (<20 HU and >20 HU) and enhancement >15 HU could increase the accuracy to 96.7%.
Conclusion: One-fifth of RCCs did not reach the standard enhancement threshold that were mostly found in nonclear cell subtype. Especially, when the mass was larger than 7 cm or involved nonclear cell RCCs, the enhancement threshold >15 HU must be carefully used for diagnosis. Using a noncontrast phase regardless HU combined with enhancement >15 HU could improve the accuracy of RCC diagnosis.

Keywords: renal cell carcinoma, attenuation, Hounsfield unit, kidney, cancer

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Introduction

Renal cell carcinoma (RCC), the most common kidney cancer in adults, comprises approximately 90% of kidney cancers.[1] Incidence of RCC is 3.8 cases per 100,000 populations, while the incidence in Thailand is 1.6%.[2] Since 1971, incidence of renal mass has significantly increased due to increase use of Computed Tomography (CT) scan to diagnose other symptoms[3], particularly unenhanced CT has been increasingly used for kidney stones and CT colonography.[4]

CT scan with contrast study has been extensively recognized as a potential tool for diagnosis of RCC. Renal mass that is enhanced in nephrogenic phase on CT more than 15 Hounsfield units (HU) should be suspected of RCC.[5] Currently, many studies illustrated that an enhancement level above 15 HU indicated a false negative result for RCC diagnosis. A Canadian study found that around 17.2% of RCCs did not reach the 15 HU enhancement on CT studies.[6] Another study found that 15% of more than 15 HU enhancements in surgically resected renal masses were benign lesions.[7] Unenhanced CT has been increasingly used to evaluate other conditions, especially in patients who have chronic kidney diseases or allergy to contrast. Many studies concerning the noncontrast CT have suggested the range of HU more than 70 HU or less than 20 HU indicated benign lesion and required no further workup.[8-10]

This study aimed to determine whether RCC enhanced in CT is below the standard enhancement threshold and to analyze the HU range of RCC using the noncontrast CT where possible malignancy should be considered.

Methods

This retrospective descriptive study was approved by the Institutional Review Board of the Royal Thai Army Medical Department and acquisition of consent was waived (R041h/60). Using the Urology Department's database, Thai patients with renal cell carcinoma who were operated on, both radical and partial nephrectomy, at Phramongkutklao Hospital from January 2007 to December 2017 were enrolled in this study. The inclusion criteria included patients with pathologically proven RCCs with the size of renal lesion more than 1 cm. A related study has shown that renal lesions of less than 1 cm were too small to adequately characterize.[11] To reduce misunderstanding between each RCC and CT imaging, patients who had more than one mass in each kidney, polycystic kidney disease or von Hippel Lindau disease were excluded. The demographic data presenting symptoms and cell type of RCC were collected.

CT technique and interpretation

All patients were imaged with CT scanner (Brilliance CT 64, Phillips) after an intravenous bolus of 120 mL of contrast material with rate 3 mL/sec. Four phases of CT scan were acquired: unenhanced, corticomedullary, nephrographic and delayed phase. The CT studies were reviewed by a radiologist who was specialized in genitourinary imaging and was blinded to the final diagnosis. Renal masses were measured by placing similarly sized regions of interest (ROI), between 25 to 100 mm2 and avoiding areas of focal calcification and extreme periphery of the tumor to minimize effects from surrounding normal tissue. The mean HU were corrected in each ROI in the noncontrast and nephrogenic phase systematically as shown in **Figure 1.**

Statistical analysis

Mean HU in the noncontrast, contrast and enhancement were collected. Fisher's exact test was used to identify the affecting factor of the attenuation enhancement more and or less than 15 HU. Using logistic regression to analyze the factors that affected enhancement more than 15 HU, McNemar's test was used to see differentiation of sequence using HU between the noncontrast and enhancement in RCCs. Statistical analysis was performed using SPSS Software, Version 16.0 (SPSS Inc., Chicago, IL, USA).

A total of 152 patients with pathologically proven RCC included 37 women and 115 men, ages ranging from 31 to 89 years with mean age of 61 years. Of these, 66 patients (43.4%) had incidental findings including 130 (85%) clear cell RCC, 17 (11%) papillary RCC, 2 (1%) chromophobe RCC and 3 (2%) other types. The attenuation values, mean±SD, were 32.54±8.02 HU in the noncontrast CT, 71.26±33.10 HU in the contrast CT and 38.72±30.82 for the enhancement as shown in **Table 1**.

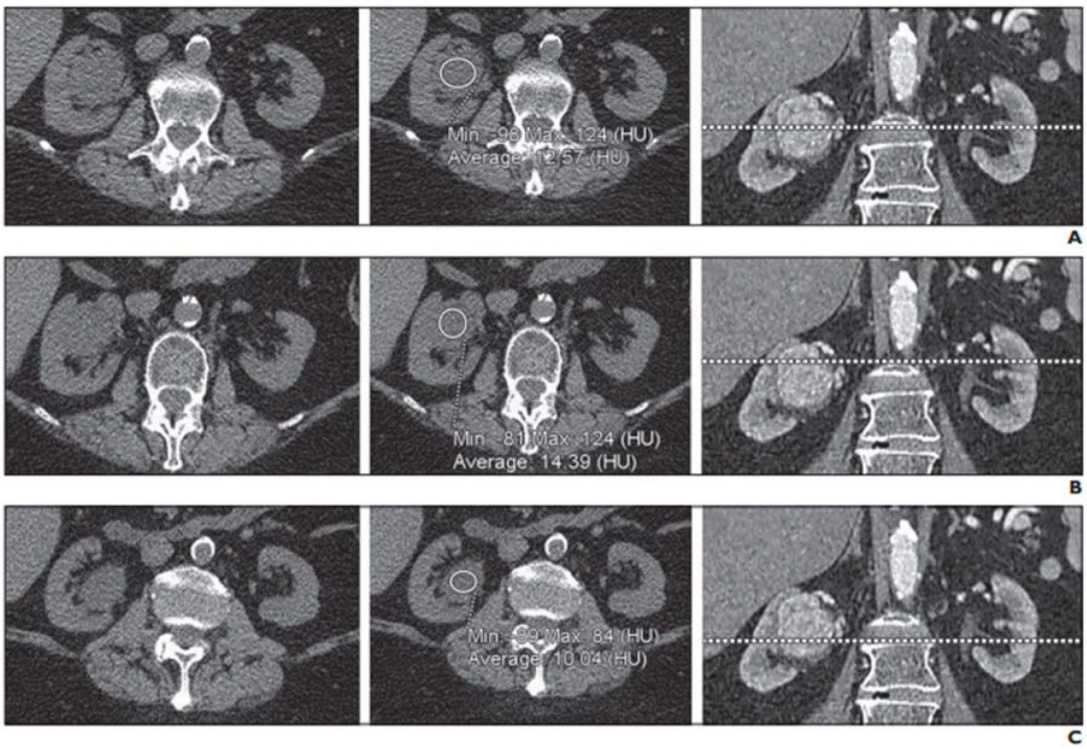

Figure 1. shows the regions of interest measurement (ROI) with separate renal mass in 3 parts by coronal image. **Picture A:** region of interest 1 is the mid part of renal mass. ROI was measured in Hounsfield attenuation in the noncontrast axial image. **Picture B:** region of interest 2 is midway between the middle and cranial margin. ROI was measured in Hounsfield attenuation in the noncontrast axial image. **Picture C:** region of interest 3 is midway between the middle and caudal margin. ROI was measured in Hounsfield attenuation in the noncontrast axial image. ROI was measured similar to the nephrogenic phase. Average attenuation of three measurements were recorded for each tumor.

Table 1. Clinical and pathological characteristics of patients

Characteristics		n = 152 (%)
Age (years)	Mean±SD	61.0±12.4
Gender	Male	115 (75.7)
	Female	37 (24.3)
Symptoms	Yes	86 (56.6)
	No	66 (43.4)
Histologic	Clear cell RCC	130 (85.5)
	Papillary RCC	17 (11.2)
	Chromophobe RCC	2 (1.3)
	Others	3 (2.0)
Location	Right	70 (46.0)
	Left	82 (54.0)
Size	<4 cm	35 (23.0)
	4 - 7 cm	38 (25.0)
	>7 cm	79 (52.0)

Table 1. Clinical and pathological characteristics of patients (Continued)

Characteristics		n = 152 (%)
Mass calcification	Yes	40 (26.3)
	No	112 (73.7)
Mass characteristic	Homogenous	40 (26.3)
	Heterogenous	112 (73.7)
Pattern	Endophytic	34 (22.4)
	Exophytic	118 (77.6)
Non-contrast HU	Mean±SD	32.54±8.02
	Median (min, max)	32.00 (13.30, 57.23)
Contrast HU	Mean±SD	71.26±33.10
	Median (Min, Max)	62.48 (16.87, 202.80)
Enhancement HU	Mean±SD	38.72±30.82
	Median (Min, Max)	32.12 (-3.20, 156.97)

*SD – standard deviation, RCC – renal cell carcinoma, HU – Hounsfield unit

We found that 31 RCCs did not reach the enhancement threshold at >15 HU. As a result, 20.4% of the RCCs could not be diagnosed because of no enhancement in the nephrogenic phase. Both cell type and size of tumor that affected enhancement were statistically significant (p <0.001). Using multiple logistic regression, enhancement of clear cells had 25 times greater than that of non-clear cells (AOR = 25.71, 95% CI=6.23-101.1). The size of tumor less than 7 cm also had 11 times greater enhancement. (AOR=11.52, 95% CI=2.846.6) after having adjusted with clear cell histologic subtype. (**Table 2**). Significant differences in proportion of different subtypes of RCC that did not reach the 15 HU enhancement threshold were observed, namely, 100% chromophobe RCC, 58.8% papillary RCC and 13.1% clear cell RCC (p<0.001). Using HU cut points in the noncontrast study, no significant differences between cell type groups were observed. (**Table 3**)

This study also analyzed the attenuation range of RCCs in the noncontrast CT. The minimum and maximum attenuations were 13.30 and 57.23 HU, respectively (32.54±8.02 HU). Minimum attenuation less than 20 HU was 23 (15%) of the tumor, and no tumor had a maximum attenuation greater than 60 HU. CT attenuation between 20 and 60 HU accounted for 84.9% of the RCCs. Accuracy of the standard 15 HU enhancement threshold was 79.6% while 20 to 60 HU in the noncontrast CT was 84.9%. The 20 to 60 HU attenuation gave more accuracy for RCC diagnosis than that of the standard contrast enhancement (**Table 4**).

DISCUSSION

Due to increased use of CT, more RCCs have been detected. Related studies have proposed where enhancement thresholds of 15 HU might lead to 17.2% misdiagnosis of RCCs especially in papillary RCC.[6] Therefore, this study aimed to evaluate the accuracy of the criteria set by enhancement of more than 15 HU of pathologically proven RCCs in Thai patients. The result was similar to the related study that 20.4% of RCCs did not reach 15 HU enhancement.

The classification of RCC is based on histopathology. Histological subtype is related to different tumor characteristics and cancer prognosis. Several studies found that attenuation values can differentiate RCC subtypes, especially in clear cells and other subtypes.[14] This study found that clear cell RCC appeared to be better enhanced than nonclear cell RCC. Due to high vascular supply and alveolar structure of histologic studies, the clear cell subtype showed higher enhancement of HU when compared with other subtypes.[15,16]

Table 2. Multiple logistic regression for factors of enhancement attenuation

	Enhancement <15 HU (%)	Enhancement ≥15HU (%)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age (years) (mean±SD)	60.3±13.6	61.2±12.1	0.702		
Sex					
Male	21 (18.3)	94(81.7)	0.250		
Female	10 (27.1)	27 (72.9)			
Symptoms					
Yes	21 (24.5)	65 (75.5)	0.160		
No	10 (15.2)	56 (84.8)			
Histologic type					
Clear cell RCCs	17 (13.1)	113 (86.9)	**<0.001**	25.17 (6.23- 101.1)	**<0.001**
Non clear cell RCCs	14 (63.6)	8 (36.4)			
Location					
Right	17 (24.3)	53 (75.7)	0.296		
Left	14 (17.1)	68 (82.9)			
Size					
< 7 cm	6 (9.2)	67 (91.8)	**<0.001**	11.52 (2.8-46.6)	**0.001**
≥ 7 cm	25 (31.6)	54 (68.4)			
Size					
< 4 cm	4 (11.4)	31 (88.6)	0.133		
≥ 4 cm	27 (23.1)	90 (76.9)			
Mass Calcification					
No	21 (28.8)	91 (81.2)	0.701		
Yes	10 (25.0)	30 (75.0)			
Mass characteristic					
Homogenous	6 (15.0)	34 (85.0)	0.324		
Heterogenous	25 (23.1)	87 (76.9)			
Pattern					
Endophytic	3 (8.8)	31 (91.2)	0.057		
Exophytic	28 (23.7)	90 (76.3)			

*SD – standard deviation, RCCs – renal cell carcinoma, HU – Hounsfield unit

Table 3. Attenuation and enhancement of Hounsfield unit in subtype of renal cell carcinoma

	Cell type (%)				*p*-value*
	Clear cell RCC	Papillary RCC	Chromophobe RCC	Others	
Enhancement					**<0.001**
<15 HU	17 (13.1)	10 (58.8)	2 (100.0)	2 (66.7)	
>15 HU	113 (86.9)	7 (41.2)	0	1 (33.3)	
Non-contrast					0.457
<20 HU	21 (16.2)	1 (5.9)	0	1 (33.3)	
>20 HU	109 (83.8)	16 (94.1)	2 (100.0)	2 (66.7)	

*Fisher's exact test

Table 4. Accuracy of using attenuations between noncontrast and enhancement in RCC

	Enhancement>15(%)	Enhancement<15(%)	Total
Non-contrast>20	103 (67.8)	26 (17.1)	129 (84.9)
Non-contrast<20	18 (11.8)	5 (3.3)	23 (15.1)
Total	121(79.6)	31 (20.4)	152 (100.0)

McNemar's test=0.291

Other significant affecting factors enhancing threshold less than 15 HU was the tumor size. Tumor size less than 7 cm also had 11 times greater enhancement. Some studies have shown that pseudo-enhancement increases with smaller masses.[17, 18] Inversely, when the mass is larger than 7 cm or non-clear cell RCC, the use of enhancement threshold >15 HU must be carefully used for diagnosis.

The noncontrast CT has been used more frequently to diagnose disease in urologic and nonurologic conditions, in situations when patients have contraindication for contrast media. Incidental finding of renal mass is the most common extracolonic cancer identified in CT studies.[19] The role of HU in RCCs involving noncontrast CT studies has not been specified in other literature. However, several studies have shown that the mean attenuation of RCCs of noncontrast CT are within the range of 20 to 70.[20, 21] Homogenous renal mass with HU less than 20 HU or more than 70 HU can be considered benign without need for further investigation.[8-10, 22] Therefore, we used the lower range of attenuation between 20 to 60 HU in the noncontrast CT as a threshold to identify the length of pathologically proven RCC in Thai patients. Our study found that pathologically proven RCC in this range was 84.9%, similar to the study of Dustin Pooler et al.[13] Surprisingly, the results showed more accuracy than the standard enhancement (>15HU) in the nephrogenic phase at 79.6%. However, our study encountered limitations, not including the benign lesion of kidneys such as oncocytoma and angiomyolipoma in the study. As the result, we cannot conclude that the use of non-contrast with HU >20 was more accurate than enhancement in the nephrogenic phase.

Our study found that 15% of RCCs had an attenuation less than 20 HU. A related study showed that a few solid RCCs had attenuation like the water (-10 to 20 HU) on the noncontrast study, but all were clear cell subtypes with heterogeneous mass.[12] None of the RCCs had attenuation more than 60 HU which was similar to the results of the study by Jonisch et al.[9] We concluded that renal mass with an attenuation of 60 HU or higher of the noncontrast CT had a greater chance of representing a high attenuation cyst and not RCC. This study showed that most RCCs in this series could be measured at values between 20 and 60 HU with the noncontrast CT.

An unenhanced renal mass containing this range of attenuation should be carefully evaluated because of malignancy risk.

Accuracy of the standard 15 HU enhancement threshold and 20 to 60 HU in the non-contrast CT were 79.6% and 84.9%, respectively. Altogether 20 to 60 HU attenuation gave more accuracy for RCC diagnosis than the standard contrast enhancement. To improve the accuracy of RCC diagnosis, the combined use of both noncontrast attenuation group (<20 HU and >20 HU) and enhancement >15 HU could increase the accuracy to 96.7%.

In clinical practices, when malignancy from an imaging study is unsuspected (<20 HU or enhancement <15 HU), an active surveillance strategy was used to follow up the patient. As a result, tissue diagnosis from this group of patients could not be obtained. In this study, only one radiologist reviewed the CT scans. Thus, no inter-observers were used to examine the results of HU. Finally, our study only showed lower enhanced HU in nonclear cells compared with clear cell subtype of RCC. In future studies, comparison of HU among noncontrast, corticomedullary and nephrogenic phases could help differentiate subtypes of RCCs.

Conclusion

One fifth of RCCs did not reach the standard enhancement threshold (>15 HU). Clear cell RCCs and small renal mass (<7 cm) had more chance to receive enhancement of HU than those of the other groups. Inversely, when the mass was >7 cm or nonclear cell RCC, the use of enhancement threshold >15 HU must be carefully used for diagnosis. The renal lesion in the noncontrast CT for which attenuation ranged from 20 to 60 HU should be carefully evaluated because of malignancy risk. Using a noncontrast phase regardless HU combined with enhancement >15 HU could improve the accuracy of RCC diagnosis.

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Conflict of interest

The authors have no conflicts of interest to declare.

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