

Quantitative Differentiation of Renal Cell Carcinoma From Fat-Poor Angiomyolipoma and Between Renal Cell Carcinoma Subtypes by Using Three-Phase MDCT

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Background: Renal cell carcinoma (RCC) can be differentiated from angiomyolipoma by detection of macroscopic fat at multidetector computed tomography (MDCT). Measurement of enhancement at MDCT help classifying between RCC subtypes, which possibly predict tumor prognosis.

Objective: Retrospectively assess whether quantitative measurements (percentage enhancement ratio [PER] and absolute washout ratio [AWR]) of renal mass enhancement during three-phase MDCT help differentiating RCC from fat-poor angiomyolipoma and other RCC subtypes.

Methods: The retrospective review of the preoperative three-phase MDCT (unenanced, corticomedullary, and early excretory phases) performed between January 2008 and July 2017, a total of 75 renal lesions (74 consecutive patients) were assessed for attenuation values in each phase. The enhancement values (PER and AWR) were compared by ANOVA tests. Cutoff analysis of enhancement values was performed to determine optimal threshold for each histologic subtype.

Results: The attenuation value of fat-poor angiomyolipoma was significantly higher than clear cell RCCs in unenhanced phase ($P = .02$). The PER of the clear cell RCCs was significantly lower than that of papillary RCCs, chromophobe RCCs, and fat-poor angiomyolipomas ($P < .001$). The AWR of the clear cell RCCs showed significantly greater than that of papillary RCCs and fat-poor angiomyolipoma ($P < .001$). The PER and AWR thresholds for differentiating RCCs from fat-poor angiomyolipoma were 93.0 and 31.6 with accuracy of 74.7% and 77.3%, respectively.

Conclusions: Quantitative measurement of enhancement (PER and AWR) might help differentiating RCCs from fat-poor angiomyolipoma, and differentiating clear cell RCCs from papillary RCCs.

Keywords: Renal cell carcinoma, Angiomyolipoma, Fat-poor angiomyolipoma, MDCT

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Introduction

Renal cell carcinoma (RCC) was the second most common urologic neoplasm in the United States in 2012. It has accounted for approximately 5% of all cancers in men and 3% in women.¹ The incidence of renal cancer in Thailand was less common than the other organs (0.28% - 0.54%) and approximately 40% of all renal cancers in Thailand were RCCs.²⁻⁶

In 2004, World Health Organization (WHO) classified RCC subtypes into clear cell RCC, papillary RCC and chromophobe RCC. The most common subtype is clear cell RCC (70% - 80%), followed by papillary (14% - 17%) and chromophobe (4% - 8%) RCC.⁷⁻⁹ The chromophobe RCC had the best prognosis among those subtypes. The overall 5-year survival rate of the clear cell RCC, papillary RCC and chromophobe RCC were 55% - 60%, 80% - 90%, and 90%, respectively.^{10, 11}

Another lesion, angiomyolipoma, a benign tumor that accounts for 0.3% - 3.0% of renal tumors, was easily diagnosed on the basis of the finding of bulk fat at multidetector computed tomography (MDCT).¹² However, approximately 3% - 4% of angiomyolipoma exhibited no detectable fat at MDCT (so called fat-poor angiomyolipoma) and was almost indistinguishable from other renal tumors including RCC.¹³⁻¹⁶

Differentiation between RCC subtypes and fat-poor angiomyolipoma was usually made on the histologic findings of the surgically removed tumor. For all these reasons, preoperative diagnosis by imaging would be of great value to avoid unnecessary surgery in patients with benign lesions and to determine the treatment planning, such as determining the degree of preoperative evaluation and the extent of surgery.

The previous study had performed differentiation of lipid-poor angiomyolipoma from RCC by using multiphasic contrast enhanced CT. However, the previous study had showed variable results, causing limitation of this utility. These conflicting results might be from the different RCC subtypes, which showed varying enhancement patterns.^{17, 18}

Many studies also had focused on RCC subtypes differentiation by using degree of enhancement. Some studies

had shown that the degree of enhancement of clear cell RCC was greater than other RCC subtypes. However, this finding has limited clinical value because all renal phases were not analyzed, clinically relevant performance parameters were not analyzed in detail, and the fat-poor angiomyolipoma was not assessed in most of these studies.^{13, 16, 19}

Recent studies have attempted to quantitatively measure the washout characteristics for differentiation between RCC and fat-poor angiomyolipoma. Washout characteristic refers to the reduction of the attenuation values of the lesions on CT scan during a variable period subsequent to the intravenous injection of a bolus of contrast material. These studies based on the biodistribution of contrast medium is determined by the vascular perfusion level of different tissues and the capillary permeability. Most of the malignant tumors have a larger extracellular space and a higher degree of vascular perfusions, which resulted in intense enhancement in early enhanced CT scans and larger washout in delay enhanced CT scans. In contrast to most of the angiomyolipomas, they consisted of distorted blood vessel and blood sinusoids which resulted in retention of contrast medium in delay enhanced CT scans.²⁰ Similar temporal attenuation changes have been quantitatively measured to differentiate adrenal adenoma from carcinoma on the basis of either absolute percentage washout or relative percentage washout in two- and three-phase CT protocols.²¹ However, the quantitative measurements of the degree of enhancement and washout characteristic have not been widely reported for RCC subtypes and fat-poor angiomyolipoma.

The purpose of this study was to retrospectively assess whether quantitative enhancement measurement at three-phase MDCT can help differentiate RCC from fat-poor angiomyolipoma and of clear cell RCC from other RCC subtypes.

Methods

Study Population

This retrospective cross-sectional study included patients with diagnosis of renal neoplasm from database of Ramathibodi Hospital from January 2008 to July 2017,

who had undergone three-phase MDCT and the images had to be available in standard digital format. They had to have the histopathologically proved clear cell RCC, papillary RCC, chromophobe RCC, or angiomyolipoma. Patients with unavailable demographic data for review and presence of identifiable macroscopic fat within the mass on CT images for angiomyolipoma were excluded.

Finally, a study cohort of 75 renal lesions in 74 consecutively registered patients was compiled. One patient had 2 lesions with pathologically proved angiomyolipoma.

MDCT Examination

All patients underwent preoperative imaging evaluation with contrasted enhanced three-phase MDCT. The CT examinations were performed with a 64-, or 320-MDCT scanner (SOMATOM Sensation 64, Siemens Healthineers, Erlangen, Germany; and Aquilion ONE 320, Canon Medical System Corp, Tokyo, Japan). The scanning parameters included 120 kVp, variable tube current, 3.0-mm section collimation, and a section interval of 3 mm depending on the protocol used. Typically, 90 - 100 mL of nonionic iodinated contrast material was power injected at a rate of 2 - 3 mL/s followed by a saline chaser. Oral and rectal contrast material were variably administered depending on the protocol used. Bolus tracking software (CARE Bolus, Siemens Healthineers, Erlangen, Germany; SUREStart, Canon Medical System Corp, Tokyo, Japan) was used, corticomedullary and early excretory phase scans were obtained 40 - 50 seconds and 180 - 300 seconds after initiation of contrast administration.

Image Analysis

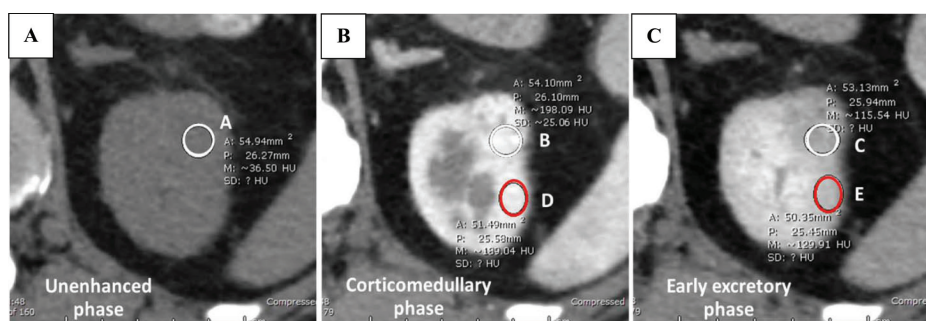
All preoperative CT images were retrospectively reviewed independently at the picture archiving and communications system (PACS) work station by a 3rd-year diagnostic radiology trainee and an 8-year experience abdominal radiologist blinded to the pathological diagnosis. Before reviewing the CT images, the reviewer placed a region of interest (ROI) of approximately 0.5 - 1.0 cm² on the most avidly enhancing part of a heterogeneously enhancing lesion or in the center of a homogeneously enhancing lesion. The attenuation value of the renal cortex was also measured as a reference to indicate the iodine load (Figure 1). The largest diameter of each lesion was measured on axial or coronal images.

The enhancement values-percentage enhancement ratio and absolute washout ratio-on unenhanced, corticomedullary, and early excretory phase images were calculated with the following formulas: $PER_{CM/EE} = 100 \times (AE_{CM/EE} / LE_{CM/EE})$; and $AWR = 100 \times (LE_{CM} - LE_{EE}) / (LE_{CM} - LE_U)$; in which PER is percentage enhancement ratio, AWR is absolute washout ratio, U is unenhanced phase, CM is corticomedullary phase, EE is early excretory phase, AE is average enhancement of renal cortex adjacent to the lesion and LE is enhancement of the lesion. All attenuation measurements were in HU.^{22, 23}

Ethical Considerations

The local institutional review board approved this retrospective data collection study in agreement with the ethical rules (MURA2016/805).

Figure 1. Attenuation Value Measurements of the Renal Lesion and Renal Cortex in Different Phases



White circle indicates lesion ROI, and red circle indicates cortex ROI.

A, Unenhanced phase; B, Corticomedullary phase; C, Early excretory phase.



Statistical Analysis

For qualitative analysis, this study used paired samples correlations to determine the interobserver error between the 2 reviewers. Mann-Whitney test was used to compare the mean attenuation values of clear cell RCCs with those of papillary RCCs, chromophobe RCCs, and fat-poor angiomyolipomas in the unenhanced, corticomedullary, and early excretory phases of enhancement. This study used ANOVA test to differentiate the enhancement values (PER and AWR) of clear cell RCC from those of the other 3 groups. Cutoff analysis was performed to determine the optimal threshold level of enhancement values. For each threshold level, calculated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were performed. Standard binomial receiver operating characteristic (ROC) curves were generated for differentiation of clear cell RCC from the other 3 groups by using of maximum likelihood estimation. Values of $P \leq .05$ was considered statistically significant.

Results

Patient and Lesion Characteristics

During January 2008 and July 2017, this cohort study included 74 consecutively registered patients (48 men, 26 women; median [range] age, 57.5 [30 - 89] years) with 75 renal lesions. Pathological specimens were acquired most commonly after partial or radical nephrectomy and less commonly after excision. Of these 75 renal lesions, 54 lesions were clear cell RCC; 11 lesions were papillary RCC; 3 lesions were chromophobe RCC; and 7 lesions were fat-poor angiomyolipoma. Mean lesion size was 5.6 cm for clear cell RCC and papillary RCC, 7.1 cm for chromophobe RCC, and 2 cm for fat-poor angiomyolipoma (Table 1).

Analysis of Attenuation Values

The mean attenuation values of renal lesions and renal cortices in each phase between 2 reviewers were determined (Table 2). There was no significant difference in the attenuation value measurements of the renal lesions and renal cortices in each phase between 2 reviewers with

correlations of 0.86, 0.97, and 0.90 of renal lesions in unenhanced, corticomedullary and early excretory phases, and with correlations of 0.96 and 0.92 of renal cortices in corticomedullary and early excretory phases, respectively. Thus, the average attenuation values between reviewer 1 and reviewer 2 of renal lesions and renal cortices were used to represent the lesion and cortex attenuation values in each phase.

The mean attenuation values of renal lesions and renal cortices in each phase were determined (Table 3). The attenuation values of the fat-poor angiomyolipoma showed significantly higher than those of clear cell RCCs in unenhanced phase (42.7 vs 33.6 HU; $P = .02$). In contrast, there was no significant difference in mean attenuation of the clear cell RCCs compared with those of other RCC subtypes.

The mean attenuation values of clear cell RCCs, chromophobe RCCs and fat-poor angiomyolipoma appeared greatest in the corticomedullary phase. In contrast, the mean attenuation value of the papillary RCCs appeared greatest in early excretory phase. The mean attenuation value of the clear cell RCCs in the corticomedullary phase showed significantly greater than those of papillary RCCs (133.1 vs 46.9 HU; $P < .001$), those of chromophobe RCCs (133.1 vs 82.7 HU; $P = .009$), and those of fat-poor angiomyolipoma (133.1 vs 94.5 HU; $P = .002$). The mean attenuation value of the clear cell RCCs in the early excretory phase showed only significantly greater than those of papillary RCCs (82.5 vs 54.8 HU; $P < .001$).

Analysis of Enhancement Values

The enhancement values of each renal lesions were determined (Table 4). The PER of the clear cell RCCs showed significantly lower than papillary RCCs (72.6 vs 130.4 HU; $P < .001$), chromophobe RCCs (72.6 vs 96.1 HU; $P = .02$), and fat-poor angiomyolipoma (72.6 vs 101.5 HU; $P < .001$). The AWR of the clear cell RCCs showed significantly greater than papillary RCCs (49.0 vs - 87.1 HU; $P < .001$), and fat-poor angiomyolipoma (49.0 vs 21.5 HU; $P < .001$). Apart from this, there was no significant difference in the AWR between clear cell RCCs

and chromophobe RCCs. The PER and AWR of angiomyolipoma and clear cell RCC in different 2 patients were shown (Figure 2).

Differentiation by Enhancement Values

It was possible to differentiate all RCCs subtypes from fat-poor angiomyolipoma with threshold level of 93.0 for PER; and 31.6 for AWR. The use of the PER threshold of 93.0 might help differentiate RCCs from fat-poor

angiomyolipomas with sensitivity of 72.1% (49/68), specificity of 100% (7/7), positive predictive values of 100% (49/49), negative predictive values of 26.9% (7/26), and accuracy of 74.7% (56/75). The use of the AWR threshold of 31.6 might be other clues for differentiating RCCs from fat-poor angiomyolipoma with sensitivity of 75.0% (51/68), specificity of 100% (7/7), positive predictive values of 100% (51/51), negative predictive values of 29.2% (7/24), and accuracy of 77.3% (58/75).

Table 1. Characteristics of Renal Lesions

Characteristic	Clear Cell RCC	Papillary RCC	Chromophobe RCC	Fat-Poor Angiomyolipoma
Number of lesions, No. (%)	54 (72%)	11 (14.7%)	3 (4%)	7 (9.3%)
Sex, No.				
Men	38	9	1	0
Women	16	2	2	7
Age, mean (range), y	58 (32 - 86)	52 (19 - 69)	55 (47 - 60)	59 (30 - 82)
Size, mean (range), cm	5.6 (1.4 - 14)	5.6 (1 - 15)	7.1 (3.8 - 12)	2 (0.4 - 5.3)
Specimen acquisition, No.				
Excision	0	1	0	2
Partial Nephrectomy	7	2	1	3
Radical Nephrectomy	47	8	2	2

Abbreviation: RCC, renal cell carcinoma.

Table 2. Mean Attenuation Values in Each Phase by Two Reviewers

Phases	Unenhanced Phase	Corticomedullary Phase		Early Excretory Phase	
		Renal Lesion	Renal Cortex	Renal Lesion	Renal Cortex
Reviewer 1	34.7	114.3	150.0	77.5	129.0
Reviewer 2	34.4	115.3	151.6	78.1	130.0
Correlation*	0.86	0.97	0.96	0.90	0.92

* The mean attenuation values in each phase between 2 reviewers were compared by using 2 paired correlations.

The correlations > 0.75 determined no significant difference between 2 reviewers.

Table 3. Attenuation Values by Histological Subtypes

Phase	Mean (range), HU			
	Clear Cell RCC (n = 54)	Papillary RCC (n = 11)	Chromophobe RCC (n = 3)	Fat-Poor Angiomyolipoma (n = 7)
Unenhanced				
Renal lesion	33.6 (14.5 - 40.5)	33.8 (17 - 71.5)	35.7 (29.5 - 41)	42.7 (38 - 58)
P value	-	.94	.69	.02

Table 3. Attenuation Values by Histological Subtypes (Continued)

Phase	Mean (range), HU			
	Clear Cell RCC (n = 54)	Papillary RCC (n = 11)	Chromophobe RCC (n = 3)	Fat-Poor Angiomyolipoma (n = 7)
Corticomedullary				
Renal lesion	133.1 (88 - 201.5)	46.9 (22.5 - 84)	82.7 (75.5 - 97)	94.5 (88.5 - 99)
<i>P</i> value	-	< .001	.009	.002
Renal Cortex	150.7 (40 - 212.5)	143 (108.5 - 195.5)	165.7 (118 - 226)	157.8 (127 - 230.5)
<i>P</i> value	-	.50	.49	.62
Early excretory				
Renal lesion	82.5 (58 - 136.5)	54.8 (24 - 83)	65.3 (55.5 - 72)	83.5 (73.5 - 93)
<i>P</i> value	-	< .001	.06	.86
Renal cortex	128.5 (75.5 - 193)	132.7 (101 - 176.5)	129.2 (117 - 151.5)	132.2 (107 - 188)
<i>P</i> value	-	.61	.97	.72

Abbreviation: RCC, renal cell carcinoma.

Table 4. Enhancement Values by Histological Subtypes

Phase	Mean (range), HU			
	Clear Cell RCC (n = 54)	Papillary RCC (n = 11)	Chromophobe RCC (n = 3)	Fat-Poor Angiomyolipoma (n = 7)
PER				
Values	72.6 (34.7 to 125.4)	130.4 (84.5 to 186.1)	96.1 (90 to 110.7)	101.5 (94.3 to 117.6)
<i>P</i> value	-	< .001	.02	< .001
AWR				
Values	49.0 (21.4 to 67.7)	-87.1 (-254.5 to 29.4)	37.0 (20.3 to 51.3)	21.5 (9.9 to 30.9)
<i>P</i> value	-	< .001	.15	< .001

Abbreviations: AWR, absolute washout ratio; PER, percentage enhancement ratio; RCC, renal cell carcinoma.

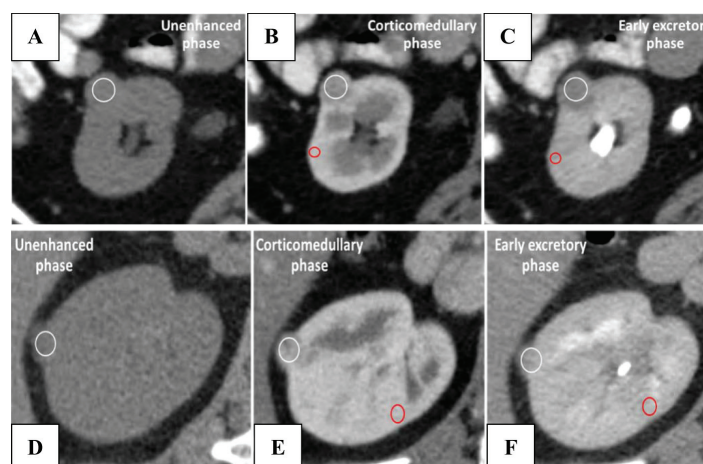
Discussion

This present study found that the mean attenuation value of the fat-poor angiomyolipomas was significantly greater than clear cell RCCs in unenhanced phase, which correspond with the previous studies.^{22,23} This result helps make confident differentiation of fat-poor angiomyolipoma from clear cell RCCs.

The mean attenuation value of the clear cell RCCs was significantly greater than that of other RCC subtypes and fat-poor angiomyolipomas in corticomedullary phase (Table 3). Reports of previous studies supported consideration of clear cell RCCs in the evaluation of high attenuation renal lesions in corticomedullary phase.^{20,22}

Using enhancement values (PER and AWR) would be helpful for improving the accuracy, especially in differentiating clear cell RCCs from papillary RCCs and fat-poor angiomyolipomas.²² This present study found that clear cell RCCs showed significantly lower PER with greater AWR as compared to those of papillary RCCs. These corresponded with the basis of peak corticomedullary enhancement with weak early excretory enhancement of the clear cell RCCs, and of weak corticomedullary enhancement with peak early excretory enhancement of the papillary RCCs.²² This present study also found that clear cell RCCs showed significantly greater AWR as compared to that of the fat-poor angiomyolipoma which

Figure 2. PER and AWR of Angiomyolipoma and Clear Cell RCC in Three-Phase MDCT



Abbreviations: AWR, absolute washout ratio; MDCT, multidetector computed tomography; PER, percentage enhancement ratio; RCC, renal cell carcinoma.

White circle indicates lesion ROI; red circle indicates cortex ROI. Axial MDCT images show three-phase enhancement of angiomyolipoma (A, B, C) and clear cell RCC (D, E, F). PER of angiomyolipoma and clear cell RCC were 116.3 and 103.3; and AWR of angiomyolipoma and clear cell RCC were 24.7 and 34.2.

were consistent with the previous study.^{20, 22} These might be explained on the basis of the different wash-in and wash-out characteristics between clear cell RCCs and fat-poor angiomyolipomas. Most of the malignant tumors had a larger extracellular space and a higher degree of vascular perfusions, which result in intense enhancement in early enhanced CT scans and larger washout in delay enhanced CT scans. In contrast to the most of angiomyolipomas, they consisted of distorted blood vessel and blood sinusoids which result in retention of contrast medium in delay-enhanced CT scans.²⁰

A quantitative enhancement measurement for distinguishing fat-poor angiomyolipoma from RCCs by using PER threshold of 93.0 and AWR threshold of 31.6 was advantageous for differentiating all RCC subtypes from fat-poor angiomyolipoma with high sensitivity, specificity and positive predictive value. These results helped less experienced radiologists and referring physicians make confident differentiation of RCCs from fat-poor angiomyolipoma and helped avoid unnecessary surgery in patients with benign lesions. However, these thresholds showed low negative predictive value, so an additional management such as interval follow-up

or tissue diagnosis in patient with greater PER or lower AWR recommended than the aforementioned threshold.

This present study had three limitations. First, this study was retrospectively design and might introduce selection bias. Second, there had a relatively small number of subtype lesions, especially chromophobe RCCs and fat-poor angiomyolipoma. And third, all of these lesions were not scanned with the same CT scanner. Although this study suggested that fat-poor angiomyolipomas might be non-invasive differentiation from the RCCs and differentiation of clear cell RCCs from papillary RCCs on the basis of the combinations of PER and AWR, these results should be further studied in the larger sample of prospective studies.

Conclusions

This present study showed that quantitative enhancement measurement by using PER and AWR might help differentiating RCCs from fat-poor angiomyolipoma with PER and AWR thresholds of 93 and 31.6 and differentiating clear cell RCCs from papillary RCCs subtypes.

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การแยกมะเร็งไตชนิด Renal Cell Carcinoma ออกจากชนิด Fat-Poor Angiomyolipoma และการแยกชนิดกลุ่มย่อยของมะเร็งไตชนิด Renal Cell Carcinoma โดยใช้ภาพเอกซเรย์คอมพิวเตอร์ 3 ระยะ

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บทนำ: ภาพเอกซเรย์คอมพิวเตอร์สามารถแยกมะเร็งไตชนิด Renal cell carcinoma (RCC) ออกจากชนิด Angiomyolipoma ได้โดยการเห็นไขมันในก้อนที่ไต ลักษณะ Enhancement ของก้อนในภาพเอกซเรย์คอมพิวเตอร์ช่วยแยกชนิดกลุ่มย่อยของมะเร็งไตชนิด RCC บางชนิดได้ ซึ่งจะช่วยพยากรณ์การดำเนินของโรคมะเร็งไต

วัตถุประสงค์: เพื่อศึกษาการวัดค่า Percentage enhancement ratio (PER) และ Absolute washout ratio (AWR) ของเนื้องอกไตจากภาพเอกซเรย์คอมพิวเตอร์ 3 ระยะ (Three-phase multidetector computed tomography [MDCT]) ในการช่วยแยกมะเร็งไตชนิด RCC ออกจากชนิด Fat-poor angiomyolipoma และ RCC ชนิดอื่น

วิธีการศึกษา: การศึกษาภาพเอกซเรย์คอมพิวเตอร์ 3 ระยะ แบบย้อนหลัง ในผู้ป่วยที่มีเนื้องอกของเนื้อไตก่อนผ่าตัดระหว่างเดือนมกราคม พ.ศ. 2551 ถึงเดือนกรกฎาคม พ.ศ. 2560 มีผู้ป่วยจำนวน 74 คน (เนื้องอกของไต 75 ชิ้น) เนื้องอกของไตได้รับการวัดค่า Enhancement ในทั้ง 3 ระยะ (Unenhanced phase, Corticomedullary phase, Early excretory phase) จากนั้นคำนวณค่า PER และ AWR เพื่อเปรียบเทียบระหว่างมะเร็งไตชนิด RCC กับชนิด Fat-poor angiomyolipoma และ RCC ชนิดอื่นนำไปสู่การหาค่า PER และ AWR ที่เหมาะสมในการใช้แยกมะเร็งไตชนิด RCC ออกจากชนิด Fat-poor angiomyolipoma

ผลการศึกษา: ค่า Attenuation ของ Fat-poor angiomyolipoma ใน Unenhanced phase สูงกว่า Clear cell RCC อย่างมีนัยสำคัญ ($P = .02$) โดย Clear cell RCC มีค่า PER ต่ำกว่า Fat-poor angiomyolipoma และมะเร็งเนื้อไตชนิด Papillary RCC และ Chromophobe RCC อย่างมีนัยสำคัญ ($P < .001$) ค่า AWR ของ Clear cell RCC มีค่าสูงกว่า Fat-poor angiomyolipoma และมะเร็งเนื้อไตชนิด Papillary RCC อย่างมีนัยสำคัญ ($P < .001$) ค่า PER และ AWR ที่เหมาะสมในการช่วยแยกมะเร็งไตชนิด RCC ออกจาก Fat-poor angiomyolipoma เท่ากับ 93.0 และ 31.6 (ความแม่นยำในการวินิจฉัยเท่ากับร้อยละ 74.7 และร้อยละ 77.3) ตามลำดับ

สรุป: การวัดค่า PER และ AWR ของเนื้องอกของไตน่าจะสามารถช่วยแยกมะเร็งไตชนิด RCC ออกจาก Fat-poor angiomyolipoma และแยกมะเร็งไตชนิด Clear cell RCC ออกจาก Papillary RCC ได้

คำสำคัญ: มะเร็งไต เซลล์ Angiomyolipoma เซลล์ Fat-poor angiomyolipoma เอกซเรย์คอมพิวเตอร์

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