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Differentiation of papillary renal cell carcinoma subtypes by imaging features of CT scan

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Objective : *To identify imaging features of CT scan for type 1 and type 2 papillary renal cell carcinomas (pRCCs); and, to define the findings that can be used to differentiate between these two subtypes.*

Materials and Methods : *Nineteen pRCC tumors recruited into this study were classified as pathology type 1 or type 2. The CT scans of these tumors were reviewed. Imaging features such as tumor size, margins, heterogeneity and enhancement were assessed; and, the findings of type 1 and type 2 tumors were compared.*

Results : *There were 7 type 1 and 12 type 2 tumors. On CT, type 1 tumors had more distinct margin than type 2 tumors (P-value = 0.001) and had more homogeneous density (P-value = 0.020). Type 2 tumors commonly had more infiltrative margins and showed enhancement to a greater degree than type 1 tumors in both corticomedullary and nephrogenic phases of enhancement (P-value = 0.011, 0.048, respectively).*

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Conclusion : *On CT, there are some significant differences imaging features between type 1 and type 2 papillary renal cell carcinomas; Type 1 tumors show more distinct margin and more homogeneous density than type 2. Type 2 tumors show greater enhancement degree than type 1 tumors in both corticomedullary and nephrogenic phases.*

Keywords : *Papillary renal cell carcinomas (pRCCs), CT scan, margin, heterogeneity, enhancement.*

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พอใจ เตชะนิธิสวัสดิ์, วิภาวี กิตติโกวิท, เกวลี ศศิวิมลพันธุ์. การจำแนกมะเร็งไตชนิดย่อยของ Papillary Renal Cell Carcinoma โดยลักษณะทางภาพเอกซเรย์คอมพิวเตอร์. จุฬาลงกรณ์เวชสาร 2559 ก.ย. –ต.ค.;60(5): 467 – 76

เหตุผลของการทำวิจัย : *คุณ Delahunt และคณะ ได้แบ่งมะเร็งไตชนิดย่อยของ papillary renal cell carcinoma ออกเป็นสองชนิดตามลักษณะทางพยาธิวิทยาคือ Type 1 และ Type 2 ซึ่งมะเร็งไตชนิดย่อยทั้งสองชนิดนี้มีความแตกต่างกันในด้านของการรักษาและการพยากรณ์โรค จึงทำให้มีผู้ทำการวิจัยบางกลุ่มต้องการที่จะแยกมะเร็งไตชนิดย่อยทั้งสองชนิดนี้ออกจากกันโดยใช้ลักษณะทางรังสีวิทยา แต่ก็ยังไม่มีการศึกษาใดที่สามารถแบ่งแยกมะเร็งไตชนิดย่อยทั้งสองชนิดนี้ได้อย่างชัดเจน จึงเป็นที่มาของการศึกษาฉบับนี้ที่พยายามจำแนกมะเร็งไตชนิดย่อยทั้งสองชนิดนี้โดยลักษณะทางภาพเอกซเรย์คอมพิวเตอร์ (CT SCAN)*

วัตถุประสงค์ : *เพื่อจำแนกมะเร็งไตชนิดย่อยของ papillary renal cell carcinoma โดยใช้ลักษณะทางภาพเอกซเรย์คอมพิวเตอร์*

รูปแบบการวิจัย : *การศึกษาข้อมูลแบบย้อนหลัง*

สถานที่ทำการศึกษา : *โรงพยาบาลจุฬาลงกรณ์ จังหวัดกรุงเทพมหานคร*

ตัวอย่างและวิธีการศึกษา : *มะเร็งไตชนิดย่อยของ papillary renal cell carcinomaจำนวนทั้งหมด 19 ก้อน จะถูกแบ่งออกเป็น Type 1 กับ Type 2 โดยพยาธิแพทย์ จากนั้นจะถูกนำมาเก็บข้อมูลในเรื่องของลักษณะทางภาพเอกซเรย์คอมพิวเตอร์โดยรังสีแพทย์ผู้มีประสบการณ์ ซึ่งข้อมูลที่เราเก็บนั้นมีดังต่อไปนี้ 1.ขนาดของก้อนมะเร็ง 2.ลักษณะขอบเขตของก้อนมะเร็ง 3.องค์ประกอบของตัวก้อนมะเร็ง (Homogeneous or Heterogeneous) และ 4.ลักษณะของก้อนมะเร็งหลังจากฉีดสารทึบรังสี*

ผลการศึกษา : *มะเร็งไตชนิดย่อยของ papillary renal cell carcinoma ถูกแบ่งออกเป็น Type 1 จำนวน 7 ก้อน และ Type 2 จำนวน 12 ก้อน เมื่อนำมาเก็บข้อมูลของลักษณะภาพทางเอกซเรย์คอมพิวเตอร์พบว่า มะเร็งชนิด Type 1 มีขอบเขตที่ชัดเจนและมีลักษณะของตัวก้อนมะเร็งเป็นเนื้อเดียวกันมากกว่า (Homogeneous) มะเร็งชนิด Type 2 อย่างมีนัยสำคัญทางสถิติ (p-value = 0.001 และ 0.020 ตามลำดับ) และในส่วนมะเร็งชนิด Type 2 จะมีการเปลี่ยนแปลงหลังจากฉีดสารทึบรังสีไปแล้วมากกว่ามะเร็งชนิดType 1 อย่างมีนัยสำคัณทางสถิติ ทั้งในcorticomedullary และ nephrogenic phases (p-value = 0.011และ 0.048ตามลำดับ)*

สรุป : *ในส่วนของภาพเอกซเรย์คอมพิวเตอร์นั้น มีลักษณะบางประการที่จะสามารถช่วยในการแยกมะเร็งไตชนิดย่อยของ papillary renal cell carcinoma ออกเป็นสองชนิดได้ (Type 1 และType 2) เช่น พบว่ามะเร็งชนิด Type 1 มีขอบเขตที่ชัดเจนและมีลักษณะของตัวก้อนมะเร็งเป็นเนื้อเดียวกันมากกว่า (Homogeneous) มะเร็งชนิด Type 2 และมะเร็งชนิดType 2ก็มีการเปลี่ยนแปลงหลังจากฉีดสารทึบรังสีไปแล้วมากกว่า Type 1 ทั้งใน corticomedullaryและ nephrogenic phases*

คำสำคัญ : *มะเร็งไตชนิดย่อยของ papillary renal cell carcinoma, เอกซเรย์คอมพิวเตอร์, ขอบเขตของก้อนมะเร็ง, องค์ประกอบของตัวก้อนมะเร็ง (Homogeneous or Heterogeneous), ลักษณะของก้อนมะเร็งหลังจากฉีดสารทึบรังสี.*

Papillary renal cell carcinoma (pRCC) is the second most frequent renal cell carcinoma (RCC) subtype, accounting for approximately 13% – 15% of all known RCC lesions.[1] The patients presented were in their third to eighth decades of life. The male-to-female ratio ranges from 2:1 to 3.9:1. As it is true for all other cell types, the majority of pRCCs are discovered incidentally during work-up of unrelated conditions. Although most pRCCs are unilateral, pRCC is the most common multifocal orbilateral renal tumor.[1]

Cytogenetic and molecular studies have revealed distinct findings in pRCC that allow differentiation from other renal epithelial tumors. [2, 3] pRCCs are characterized by a papillary, tubular or tubopapillary growth pattern. They are composed of cells arranged on a delicate fibrovascular core. The cytoplasm may be basophilic, eosinophilic, or sometimes partially clear.

Delahunt *et al*.[4] described two morphologic types of pRCC with different clinical behavior. Type 1 tumors have papillae covered by a single layer of cuboidal or low columnar cells with scanty cytoplasm and low-grade nuclei. Type 2 tumors are of a higher nuclear grade and contain more than one layer of cells with abundant eosinophilic cytoplasm. Type 2 tumors generally carry a worse prognosis than type 1 tumors.

Most pRCCs are sporadic. However, there are a few familial forms. The majority of sporadic pRCCs are characterized by trisomy of chromosomes 7 and 17, as well as loss of chromosome Y in males.[1, 2, 5] Hereditary papillary renal cell cancer syndrome, hereditary leiomyomatosis and RCC syndrome and occasionally Birt-Hogg-Dube′ syndrome are associated with pRCCs. However, Birt-Hogg-Dube′ syndrome is more commonly associated with chromophobe RCCs and oncocytomas.[6] This is in contrast to the loss of genetic material from chromosome 3 and mutations in the von Hippel–Lindau gene found in clear cell RCC (cRCC). Inactivation of the von Hippel–Lindau gene is thought to activate a hypoxic response, including an increase in angiogenic factors, which might explain the hypervascularity of cRCCs in contrast to the typical hypovascular appearance of pRCCs.

In most radiologic studies, researchers have evaluated pRCC as a single subtype.[7–11] In two radiology reports, investigators presented CT and MR images with a caption mentioning the subtypes of pRCC; there are some significant differences in imaging features between type 1 and type 2 tumors. However, they did not present the clear imaging features in CT and MRI which can differentiate between the subtypes. [12,15] In this study, we examined the differences in the contrast enhanced CT (CECT) features of types 1 and 2 pRCCs.

Materials and Methods

Subjects

We found the records 26 consecutive patients in the pathologic reporting system at King Chulalongkorn Memorial Hospital who had been diagnosed with papillary RCC between January 2005 and March 2014. This study has been approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Seventeen patients had undergone preoperative CT at our hospital and the images were available. Five patients had undergone CT in another hospital and the images were not

available, four patients with MRI studies were done were before surgery; these patients were excluded from the study. Thus, the study group consisted of 17 patients, 16 men and one woman, who ranged in age from 25 to 79 years (median, 57 years). Two patients, had two discrete tumors in the contralateral kidneys that were identified on CT. Therefore, 19 tumors were examined in this study.

Pathologic Evaluation

One experienced pathologist who was unaware of the clinical information associated with each case reviewed the slides and classified the tumors into the pathologic subtypes of pRCC: type 1 or type 2.

CT Examination

Since each CT examination was performed at different times over a period of 9 years, the patients were examined by various types of CT scanners. MDCT scan in unenhanced and triphasic contrast-enhanced CT examinations were performed in 17 patients (19 tumors). These CT images were obtained with the following parameters: 120 kVp; reconstruction interval, 2.5 mm in the corticomedullary and nephrographic phases; and reconstruction interval, 2.5 mm in the unenhanced and excretory phases. As for the contrast-enhanced studies, 100 mL of contrast material at a concentration of 300 mgI/mL was injected at a rate of 3.0 mL/s using a mechanical injector. Scanning for the corticomedullary phase was started 30 - 35 seconds after contrast injection. The nephrographic phase started 70 - 90 seconds after contrast injection, and the excretory phase started 8 - 10 minutes after contrast injection. Scanning for CT upper abdomen was started from the level of dome of right hemidiaphragm to the lower pole of kidneys.

Image Interpretation

One experienced radiologist who was unaware of the subtype of pRCC reviewed the CT images and recorded the margins and homogeneity. The margin was evaluated in the nephrographic phase or excretory phase in which the tumor margin was discriminated by the homogeneously enhanced renal parenchyma. When the tumor was interpreted as infiltrating beyond the renal parenchyma centripetally or centrifugally with irregular border, the margin was interpreted as indistinct. Infiltrative lesions defined as this lesion showed infiltrative with lobulated or irregular contact with adjacent renal parenchyma and/or distorted intrarenal structures. The reviewer measured the longest tumor diameter on the contrast enhanced scans and the CT attenuation on unenhanced images, corticomedullary phase images, and nephrographic phase images. A round region of interest was placed to cover as much solid enhanced area as possible. The relative enhancement ratio was calculated for the corticomedullary phase and nephrographic phase.

The relative enhancement ratio for the corticomedullary phase was calculated as follows:

$$[T_{CM} - T_{PRE}] / [T_{PRE}],$$

when T_{CM} is the attenuation of the tumor during the corticomedullary phase and T_{PRE} is the attenuation of the tumor before contrast administration.

The relative enhancement ratio for the nephrographic phase was calculated as follows:

$$[T_{NP} - T_{PRE}] / [T_{PRE}],$$

when T_{NP} is the attenuation of the tumor during the nephrographic phase.

Statistical Analysis

The pathologic and CT findings of the subtypes of pRCC were compared statistically. Chi-square test was used to evaluate the tumor margins and heterogeneity on CT scans. The independent samples *t*-test was used to evaluate CT attenuation on the unenhanced scans, and relative enhancement ratio. The relative enhancement ratio was compared for the 19 tumors that underwent triphasic contrast-enhanced CT examination. A *P*-value less than 0.05 was considered statistical significance.

Results

Pathologic Review

Seven tumors were classified as type 1 and twelve as type 2.

CT Findings

CT showed that type 1 tumors typically have distinct and smooth margins with homogeneous internal density (Figure 1). The margins of the type 1 tumors were more frequently distinct than those of type 2 tumors (*P*-value = 0.001) and had more homogeneous density (*P*-value = 0.020) (Table 1) (Figure 2). The mean attenuation on the unenhanced CT scans did not differ significantly for type 1 and 2 tumors (40.6 and 41.8 HU, respectively; *P*-value = 0.798) (Table 1). The tumors of both subtypes showed minimal enhancement. The mean relative enhancement ratios in the corticomedullary phase and nephrographic phase of type 2 tumors (0.75 and 1.15, respectively) were higher than those of type 1 tumors (0.18 and 0.56, respectively). The difference was significant (*P*-value = 0.011 and 0.048) (Table 1).

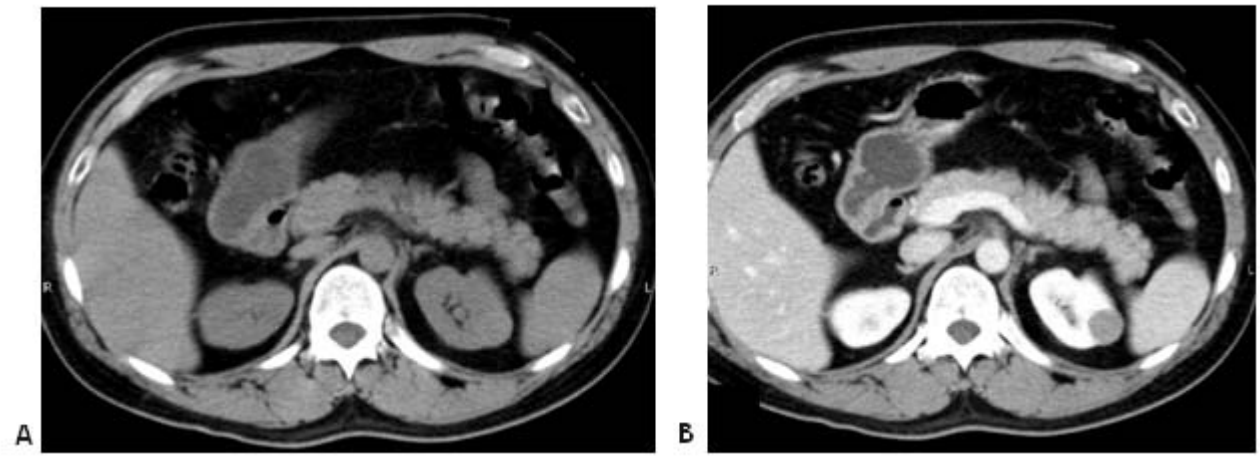

Figure 1. 39-year-old man with type 1 papillary renal cell carcinoma.

A. Unenhanced CT scan shows tumor in left kidney. Margin is distinct radiologically and internal density is homogeneou.

B. Tumor shows homogeneous hypodensity in nephrographic phase.

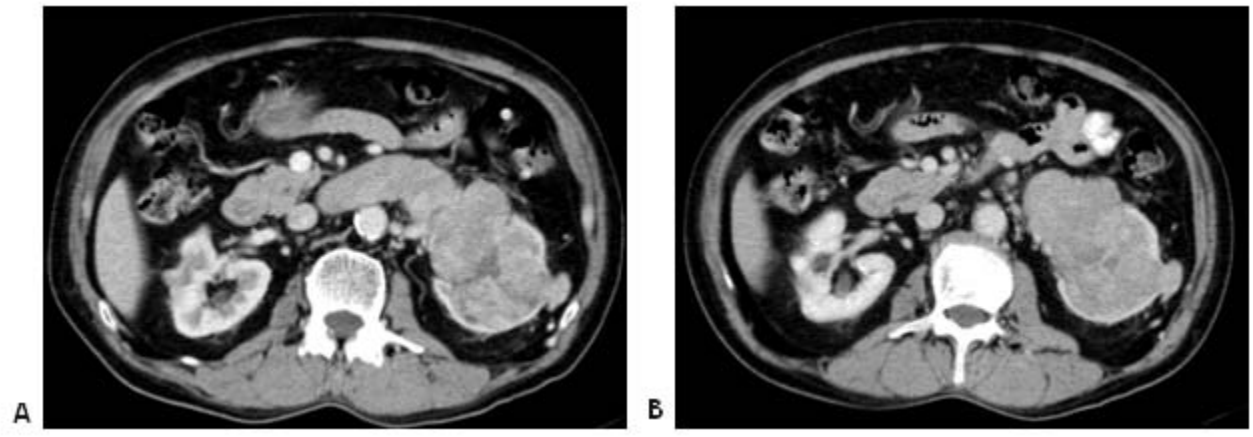

Figure 2. 73-year-old man with type 2 papillary renal cell carcinoma.

A. Large hypodense tumor in left kidney is recognized in corticomedullary phase. True margin between tumor and renal parenchyma is not well indicated; tumor extends into central region as well as perirenal space.

B. Image shows tumor margins of infiltrating component. Tumor density is some what heterogeneously hypodense.

Table 1. CT Findings of Type 1 and Type 2 Tumors.

Subtype	Margin		Heterogeneity		CT Attenuation Before Contrast Administration (HU) (n = 19)	Relative Enhancement Ratio	
	Distinct	Indistinct	Homogeneous	Heterogeneous		Corticomedullary Phase (n = 19)	Nephrographic Phase (n = 19)
Type 1	6	1	4	3	40.6 ± 8.6	0.18 ± 0.33	0.56 ± 0.52
Type 2	1	11	1	11	41.8 ± 10.6	0.75 ± 0.45	1.15 ± 0.60
p-value	0.001		0.020		0.798	0.011	0.048

Note: A p-value less than 0.05 was considered to indicate statistical significance.

Discussion

In our results, most type 1 tumors had distinct and smooth margins, whereas type 2 tumors showed significantly more indistinct margins with infiltrative growth. Type 2 tumors typically showed heterogeneous density when compared with type 1 tumors (*P*-value = 0.020). An enhancement pattern suggesting a hypovascular tumor is recognized in both subtypes of pRCC, however the enhancement pattern is useful for discriminating between the subtypes from our study. Type 2 tumors showed enhancement to a significantly greater degree than type 1 tumors in both corticomedullary and nephrogenic phases (*P*-value = 0.011 and 0.048, respectively).

Although more cases of type 2 pRCC were evaluated in our study than in previous radiology reports that evaluated enhancement patterns on CT, our study has some limitation that the number of cases was relatively small.

In recent radiology and urologic studies, researchers suggested that papillary tumors are a heterogeneous group of entities and reported that type 2 tumors show more advanced pathologic features and are associated with a poorer survival than type 1 tumors and clear cell RCC.[13, 14]

In our study, a series of pRCC cases showed a variety of CT features: type 1 tumors had more distinct and smooth tumor margin and homogeneous internal density, whereas type 2 tumors had less distinct tumor margins with infiltrative growth. Type 2 tumors showed enhancement to a greater degree than type 1 tumors in both corticomedullary and nephrogenic phases. However 2 tumors of type 1 pRCC in our study showed enhancement less than 10 HU on both corticomedullary and nephrographic phases similar on Egbert N, *et al* studied in 2013 [15] study which this finding can cause confusion distinguish with complicated cyst or cyst with high attenuation content on CT scan. Further investigation, such as MRI can help to resolve this problem. Therefore, we believe that radiologists should be aware that pRCC cases appear as two types with different pathologic behaviors.

Conclusion

In conclusion, our results indicate that CT findings may help radiologists differentiate type 1 from type 2 pRCC tumors, which have different pathologic behaviors and prognosis.

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