

Category change and incidence of malignancy in Bosniak category II, IIF and III lesions at King Chulalongkorn Memorial Hospital (KCMH)

Aniwat Sriyook*

Kewalee Sasiwimonphan*

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Background : *The widely-used classification for renal cysts is Bosniak classification which is also accepted by urologists for diagnoses and management approaches to cystic renal masses. The recent studies show variable incidences of malignancy in Bosniak category II, IIF and III lesions. Even in Bosniak category II lesion which was previously believed to be benign which had no need to follow-up has incidence of malignancy.*

Objective : *To detect the incidence of malignancy, time and rates of progression in complexity of Bosniak category II, IIF and III lesions at King Chulalongkorn Memorial Hospital (KCMH).*

Methods : *Searched the term “complex renal cyst”, “Bosniak”, “hemorrhagic cyst” and “complicated cyst” in computed tomographic (CT) and magnetic resonance imaging (MRI) studies from pictures archiving and communications system (PACS) of our institution from January 1, 2011, to December 31, 2011. Patients who had Bosniak category II, IIF and III lesions and radiological follow-up including CT, MRI and ultrasonography more than 2 years were included in this study. Re-classification of the cysts was independently performed by two blinded readers. Recorded data was sex, age, history or coexisting neoplasm, the number of cysts, characteristic of cysts, duration of follow-up, number of progression in complexity, time to progression and rate of malignancy. A total of 109 cases with 161 cysts were yielded.*

Results : A total of 161 cysts were initially reclassified to 144 Bosniak II lesions, 15 Bosniak IIF lesions and 2 Bosniak III lesions. Good agreement of classification of Bosniak category of these cysts is noted between two readers with difference experience. One lesion (6.7%) of resected Bosniak IIF was malignant. Four lesions (2.8%) in Bosniak II had progression in complexity; three lesions were reclassified as Bosniak IIF with time to progression of 1,626, 1,423 and 477 days and one lesion reclassified as Bosniak III with time to progression of 1,904 days.

Conclusion : The malignancy rates of Bosniak II, IIF and III lesions in our study are 0%, 6.7% and 0%, respectively. This may be underestimated as compared with those of prior studies due to small sample size. However, imaging surveillance of Bosniak IIF lesion is stilling recommend due to the chance of malignancy and progression of complexity in a group of Bosniak II lesion which has more case numbers.

Keywords : Bosniak category II, IIF and III lesions, malignancy rate, progression in complexity.

Correspondence to: Sasiwimonphan K. Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand.

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ของมะเร็งในถุงน้ำในไตชนิด Bosniak category II, IIF และ III ในโรงพยาบาลจุฬาลงกรณ์.
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เหตุผลของการทำวิจัย : การจัดประเภทของถุงน้ำในไตนั้นนิยมใช้ตามการจำแนกประเภทของ
Bosniak ซึ่งเป็นที่ยอมรับของศัลยแพทย์ทางเดินปัสสาวะในด้านของ
การวินิจฉัย และการจัดการเรื่องถุงน้ำในไตด้วย ในปัจจุบันนี้มี
งานวิจัยที่ศึกษาเกี่ยวกับอุบัติการณ์ของมะเร็งในถุงน้ำในไตชนิด
Bosniak category II, IIF และ III ซึ่งให้ผลค่อนข้างหลากหลาย และยัง
พบว่าแม้กระทั่งถุงน้ำในไตชนิด Bosniak category II ซึ่งเดิมเคย
เชื่อว่าเป็นถุงน้ำที่ไม่อันตรายและไม่จำเป็นต้องตรวจติดตาม กลับมี
โอกาสที่จะกลายเป็นมะเร็ง

วัตถุประสงค์ : เพื่อศึกษาอุบัติการณ์ของมะเร็ง เวลาและอัตราของการดำเนินโรคของ
ถุงน้ำในไตชนิด Bosniak category II, IIF และ III ในโรงพยาบาล
จุฬาลงกรณ์

วิธีการทำวิจัย : ค้นหาคำว่า “complex renal cyst”, “Bosniak”, “hemorrhagic cyst”
และ “complicated cyst” ที่ตรวจด้วยเครื่องเอกซเรย์คอมพิวเตอร์ (CT)
และเครื่องตรวจคลื่นแม่เหล็กไฟฟ้า (MRI) ในช่วงมกราคมถึงธันวาคม
พ.ศ. 2554 จาก Pictures archiving and communications system
(PACS) ของโรงพยาบาลจุฬาลงกรณ์ โดยทำการศึกษาในผู้ป่วยที่มี
ถุงน้ำในไตชนิด Bosniak category II, IIF และ III และมีการตรวจ
ติดตามด้วย CT หรือ MRI หรืออัลตราซาวด์อย่างน้อย 2 ปีขึ้นไป
หลังจากนั้นทำการจัดประเภทถุงน้ำในไตใหม่โดยผู้อ่าน 2 คน และเก็บ
ข้อมูลในเรื่องของเพศ, อายุ, ประวัติของมะเร็ง, จำนวนและลักษณะ
ของถุงน้ำในไต, ระยะเวลาของการตรวจติดตาม, จำนวนของถุงน้ำ
ในไตที่มีการดำเนินโรค, ระยะเวลาการดำเนินโรค และอัตราของมะเร็ง

ผลการศึกษา : จากจำนวนทั้งหมด 161 ถุงน้ำในไต ถูกแบ่งออกเป็น 144 ถุงน้ำ
ในไตชนิด Bosniak II, 15 ถุงน้ำในไตชนิด Bosniak IIF และ 2 ถุงน้ำ
ในไตชนิด Bosniak III พบว่า 1 ถุงน้ำในไตชนิด Bosniak IIF
(ร้อยละ 6.7) เป็นมะเร็ง สำหรับ 4 ถุงน้ำในไตชนิด Bosniak II
(ร้อยละ 2.8) มีการดำเนินโรค โดย 3 ถุงน้ำนั้นดำเนินโรคไปเป็น
Bosniak IIF โดยมีระยะเวลาการดำเนินโรค คือ 1,626, 1,423 และ
477 วัน และ 1 ถุงน้ำนั้นดำเนินโรคไปเป็น Bosniak III โดยมีระยะ
เวลาการดำเนินโรคคือ 1,904 วัน

- สรุป** : ในการศึกษาพบว่าอัตราการเกิดมะเร็งในถุงน้ำในไตชนิด *Bosniak II, IIF and III* คือ 0%, 6.7% และ 0% ตามลำดับ ซึ่งต่ำกว่าการศึกษา ก่อนหน้านี้ เนื่องจากตัวอย่างของการทดลองมีจำนวนน้อย แต่อย่างไร ก็ตาม พบว่าการตรวจติดตามถุงน้ำในไตชนิด *Bosniak IIF* ยังคงมีความสำคัญเนื่องจากมีโอกาสเกิดมะเร็งและการดำเนินโรคของ ถุงน้ำไตชนิด *Bosniak II* ซึ่งมีจำนวนมากกว่า
- คำสำคัญ** : ถุงน้ำในไตชนิด *Bosniak category II, IIF และ III*, อัตราของมะเร็ง, อัตราของการดำเนินโรค.

Nowadays, modern imaging modalities have increased the yields of renal cyst detection. The widely used classification for renal cysts is Bosniak classification; first described by Morton A. Bosniak in 1986.⁽¹⁾ The Bosniak renal cyst classification is also accepted by urologists for diagnoses and management approaches to cystic renal masses. The Bosniak renal cyst classification is based on the renal cyst morphology, including septa, calcification, high-density cysts, enhancement and

solid component.⁽²⁾ First, the Bosniak classification had 4 categories and had been later updated for several times. In 1993, the Bosniak classification was revised and added the category IIF into the classification which means cystic lesions that are slightly more complex than category II, but not complex enough to fulfill the criteria for category III.⁽²⁾ The Bosniak classification was latest updated in 2005 as shown in Table 1.⁽²⁾

Table 1. Bosniak renal cyst classification system.⁽²⁾

Category	Description
I	A benign simple cyst with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density and does not enhance.
II	A benign cyst that may contain a few hairline thin septa in which perceived enhancement may be present. Fine calcification or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high attenuation lesions <3 cm (so-called high-density cysts) that are well marginated and do not enhance are included in this group. Cysts in this category do not require further evaluation.
IIF	Cysts that may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Perceived enhancement of their septa or wall may be present. Their wall or septa may contain calcification that may be thick and nodular, but no measurable contrast enhancement is present. These lesions are generally well marginated. Totally intrarenal nonenhancing high-attenuation renal lesions >3 cm are also included in this category. These lesions require follow-up studies to prove benignity.
III	Indeterminate cystic masses that have thickened irregular or smooth walls or septa in which measurable enhancement is present. These are surgical lesions, although some will prove to be benign (eg, hemorrhagic cysts, chronic infected cysts, and multiloculated cystic nephroma), some will be malignant, such as cystic renal cell carcinoma and multiloculated cystic renal cell carcinoma.
IV	These are clearly malignant cystic masses that can have all the criteria of category III, but also contain enhancing soft-tissue components adjacent to, but independent of, the wall or septum. These lesions include cystic carcinomas and require surgical removal.

Many studies suggest that adding the IIF categorization has improved the accuracy of the Bosniak renal cyst classification, as evidenced by a low rate of progression in IIF lesions and a high rate of malignancy in category III lesions.⁽³⁾ In one study, the incidences of malignancy of Bosniak category I, II, IIF, III and IV lesions were 0%, 0%, 25%, 54% and 100%, respectively.⁽⁴⁾ However, the recent studies show variable incidences of malignancy in Bosniak category II, IIF and III lesions. For example, in the study of Graumann O, *et al*, they showed that the incidences of malignancy in Bosniak category II, IIF and III lesions were 12%, 12% and 61%, respectively. This means even Bosniak category II lesion which was previously believed to be benign and no need of follow-up also has incidence of malignancy.⁽⁵⁾

The purposes of this study were to detect the incidence of malignancy, time and rates of progression in the complexities of Bosniak category II, IIF and III lesions at KCMH.

Materials and Methods

Subjects

This retrospective study has been approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University. Herein, the informed consent was waived.

Pictures archiving and communications system (PACS) was used to search for the term "complex renal cyst", "Bosniak", "hemorrhagic cyst" and "complicated cyst" in computed tomographic (CT) and magnetic resonance imaging (MRI) studies of our institution from January 1, 2011 to December 31, 2011. A total of 261 cases were found.

Inclusion criteria were: Bosniak category II,

IIF and III lesions, available contrast-enhanced CT or MRI studies on PACS and radiological follow-up which included CT, MRI and ultrasonography for more than 2 years. Exclusion criteria were: non-Bosniak category II, IIF and III lesions, no contrast-enhanced study, no radiological follow-up or radiological follow-up for less than 2 years and unavailable digital imaging study on PACS. A total of 109 cases with 161 cysts were yielded (Figure 1).

Recorded data were sex, age, history or coexisting neoplasm, date of first examination, number of cysts, size of cysts, characteristic of cysts, duration of radiological follow-up, number of progression in complexity, time to progression and rate of malignancy.

CT and MRI Imaging Protocol

Because each CT and MRI examination was performed at different times over a period of 5 years, the patients were examined by using various types of CT and MRI scanners and techniques.

Multidetector CT (MDCT) scan in unenhanced and contrast-enhanced CT examinations were performed by using 120 kVp and reconstruction interval of 2.5 or 5 mm. For the contrast-enhanced studies, nephrographic phase with or without corticomedullary phase and excretory phase were performed by using 100 mL of contrast material at a concentration of 300 mgI/mL with a rate of 3.0 mL/sec using a power injector. Scanning for the corticomedullary, nephrographic and excretory phases were started at 30 - 35 seconds, 70 - 90 seconds and 10 - 15 minutes after initial contrast injection, respectively. Scanning for CT upper abdomen was started from the level of dome of right hemidiaphragm to the lower pole of kidneys.

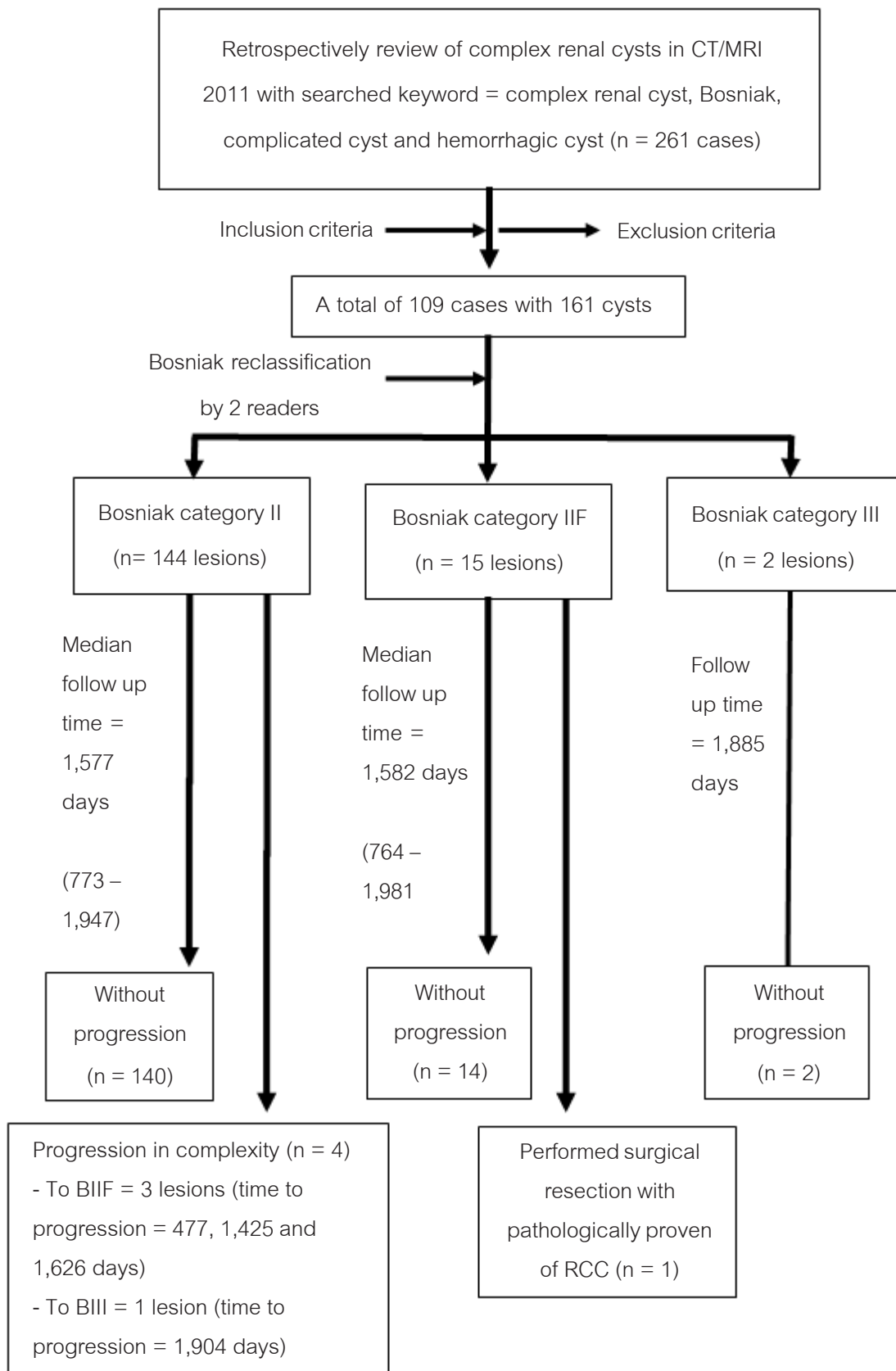


Figure 1. Flowchart of patients' inclusion and reclassification into three Bosniak groups.

MR imaging examinations were performed on 1.5T or 3T MRI systems, using a phased-array body coil. The standard imaging sequences are listed in Table 2. Gadoteratemeglumine (DOTAREM[®]) was administered with 0.2 mL/kg (0.1 mmol/kg), a rate of 2 mL/sec and flushed with 20 mL of normal saline.

Image Analysis

Bosniak reclassification of all included lesions was performed by two independently blinded readers; a radiologist with 6 years of experience in genitourinary tract imaging and a third-year radiological resident. Final reclassifications were agreed in consensus.

Statistical analysis

Three Bosniak groups were compared by using Mood's median test due to the non-normal distribution of the continuous data. Chi-square test was used to compare the percentages between the

groups. Statistical analyses were performed in SPSS version 17 (IBM Corporation, USA). *P* value that was less than 0.05 was considered statistically significantly different.

Interobserver variability for Bosniak reclassification of the lesions was measured by calculating Cohen's kappa values in Microsoft Excel 2016 (Microsoft Corporation, USA).

Results

Demographic data of patients with Bosniak category II, IIF and III lesions are shown in Table 3. Five patients had both Bosniak II and IIF lesions. Patient age was not significantly different between groups of Bosniak II, IIF and III lesions. The median ages of patients with Bosniak II and IIF lesions were 64 years (range, 27 – 86) and 65 years (range, 37 – 73), respectively. The age of the patient with Bosniak III was 61 years old.

Table 2. The standard MRI sequences.

	Dual-echo in-phase and opposed-phase spoiled gradient echo (SPGR) T1 weighted images.
	Fast spin echo (FSE) T2 weighted images with fat suppression.
	Fast spin echo (FSE) heavily T2 weighted images with fat suppression.
Axial	Steady-state free precession images with fat suppression.
	Diffusion-weighted images with B value of 500 and 1,000 sec/mm ²
	Three-dimensional (3D) spoiled gradient echo (SPGR) T1 weighted images with fat suppression (prior to and following the intravenous administration of contrast material).
	Fast spin echo (FSE) T2 weighted images with fat suppression.
Coronal	Post contrast spoiled gradient echo (SPGR) T1 weighted images with fat suppression at delayed 3 minutes.

Table 3. Demographic data, characteristic of cysts, number of and time to progression and rate of malignancy.

Number of patients	B II 98	B IIF 15	B III 1	P Value
Sex				
- Male	64 (65.3%)	9 (60%)	1 (100%)	-
- Female	34 (34.7%)	6 (40%)		-
Median age in years (range)	64 (27 – 86)	65 (37 – 73)	61	0.587*
Number of patients with history of renal cell carcinoma (%)	1 (1)	1 (6.7)	0	0.298**
Number of cysts	144	15	2	-
Median size in longest dimension in cm (range)	1.2 (0.3 – 8.3)	3.3 (0.8 – 8)	2.35 (1.4 and 3.3)	0.013*
Median HU of hyperdense cysts in plain CT	58.85 (22 – 94.1)	42.2 (34.1 – 48.7)	-	0.079*
Median F/U time in days (range)	1,576.5 (773 – 1,947)	1,582 (764 – 1,981)	1,885	0.575*
Number of progression in complexity (%)	4 (2.8%)	0	0	0.785**
Time to progression in days (range)	1,626 (II to IIF) 1,423 (II to IIF) 477 (II to IIF) 1,904 (II to III)	0	0	-
Number of malignancy (%)	0	1 (6.7%)	0	0.007**

* P value was calculated by using Mood's median test.

** P value was calculated by using Chi-square test.

In term of history or coexisting neoplasm, 98 patients with Bosniak category II had 46.9% of hepatocellular carcinoma, 14.3% of colorectal cancer, 3.1% of cholangiocarcinoma, 3.1% of gastrointestinal stromal tumor (GIST), 1% of renal cell carcinoma and 10.2% of other tumors; 14 patients with Bosniak category IIF had 14.3% of hepatocellular carcinoma, 7.1% of colorectal cancer, 7.1% of gastrointestinal stromal tumor (GIST), 7.1% of renal cell carcinoma

and 14.3% of other tumors; a patient with Bosniak category III had gastrointestinal stromal tumor. One patient with history of renal cell carcinoma post right partial nephrectomy had Bosniak II lesion in right kidney and Bosniak IIF lesion in left kidney. He also had acoexisting enhancing mass at upper pole of left kidney, which was suspicious for renal cell carcinoma. He underwent periodic surveillance imaging without surgical resection for about 3 years, which showed

stability of the two Bosniak II and IIF lesions and subsequently was lost to follow-up.

A total of 161 cysts were initially reclassified to 144 Bosniak II lesions, 15 Bosniak IIF lesions and 2 Bosniak III lesions. Significant difference in size of these lesions was observed with a median size of Bosniak II of 1.2 cm (range, 0.3 – 8.3), Bosniak IIF of 3.3 cm (0.8 – 8) and Bosniak III of 2.35 cm (1.4 and 3.3 cm).

After reclassification, patients with Bosniak II, IIF and III lesions obtained follow-up imaging at a median of 1,576.5 days (range, 773 – 1,947), a median of 1,582 days (range 764 – 1,981) and 1,885 days, respectively. Forty patients, twenty-six patients and forty-four patients received CT, MRI and ultrasonography as the latest follow-up imaging modalities respectively.

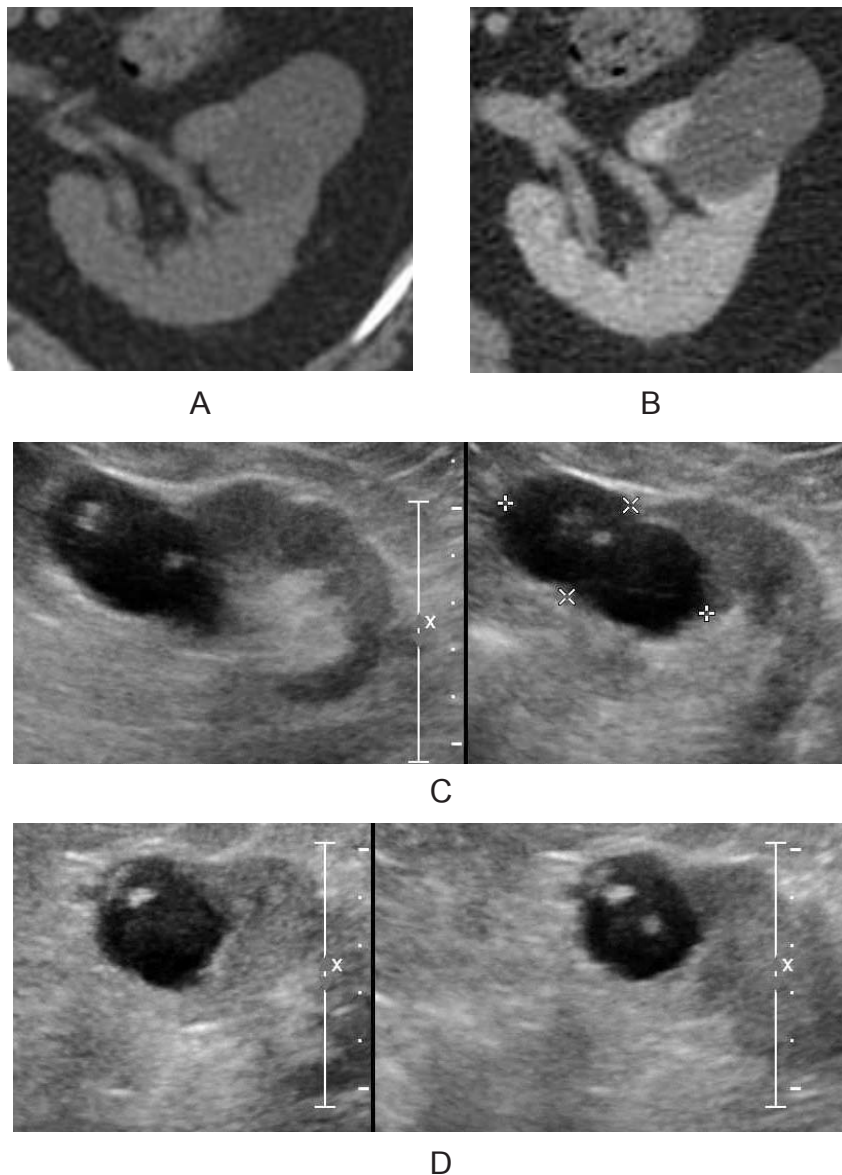


Figure 2. Baseline CT imaging of a 57-year-old male in axial plain (A.) and nephrographic (B.) phases show a 4.6 x 2.8-cm low density cyst with thin internal septation at mid-pole of left kidney, Bosniak II lesion. Follow-up ultrasonography (C. and D.) about 477 days later shows development of thick nodular calcification at internal septation of the aforementioned cyst, leading to reclassification as Bosniak IIF lesion.

Four lesions (2.8%) in Bosniak II had progression in complexity; three lesions showed interval increased thickness of calcifications at cystic wall or internal septation, leading to reclassification as Bosniak IIF with time to progression of 1,626, 1,423 and 477 days (Figure 2). One lesion showed interval increased size with developing thick irregular cystic wall, leading to reclassification as Bosniak III with time to progression of 1,904 days (Figure 3). All these lesions were managed by imaging surveillance without surgical resection. None of the patients with Bosniak IIF and III lesions had progression in complexity.

One lesion in a patient with Bosniak IIF lesion undertook surgery after receiving CT scan about 13 days and pathologically proven papillary renal cell carcinoma. The CT images of this lesion are shown in Figure 4 which shows no significant enhancement on post contrast CT scan. Imaging surveillance was obtained in this patient for about 1,641 days and revealed no evidence of recurrent tumor or metastasis.

There was substantial agreement for reclassification of Bosniak lesions between the two readers with Cohen's kappa values of 0.81 (95% CI, 0.65 – 0.97 and *P* value < 0.001).

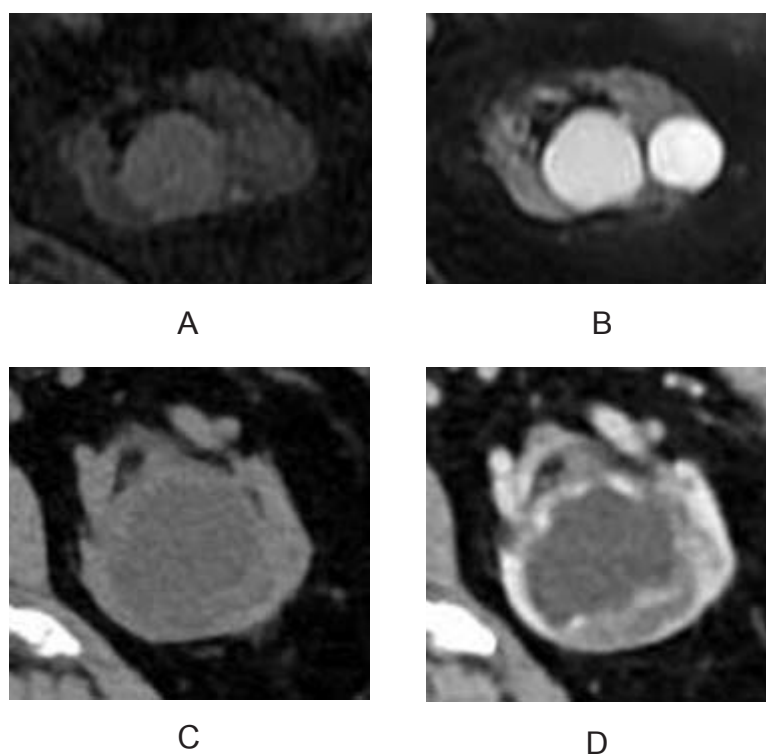


Figure 3. Baseline MRI of a 69-year-old female in axial 3D SPGR T1W (A.) and T2W (B.) show a 2.0-cm hyperintense T1W cyst at mid pole of left kidney, Bosniak II lesion. Follow-up CT imaging about 5 years later in plain (C.) and nephrographic (D.) phases show interval increased size with development of thick irregular wall of the aforementioned cyst, leading to reclassification as Bosniak III lesion.

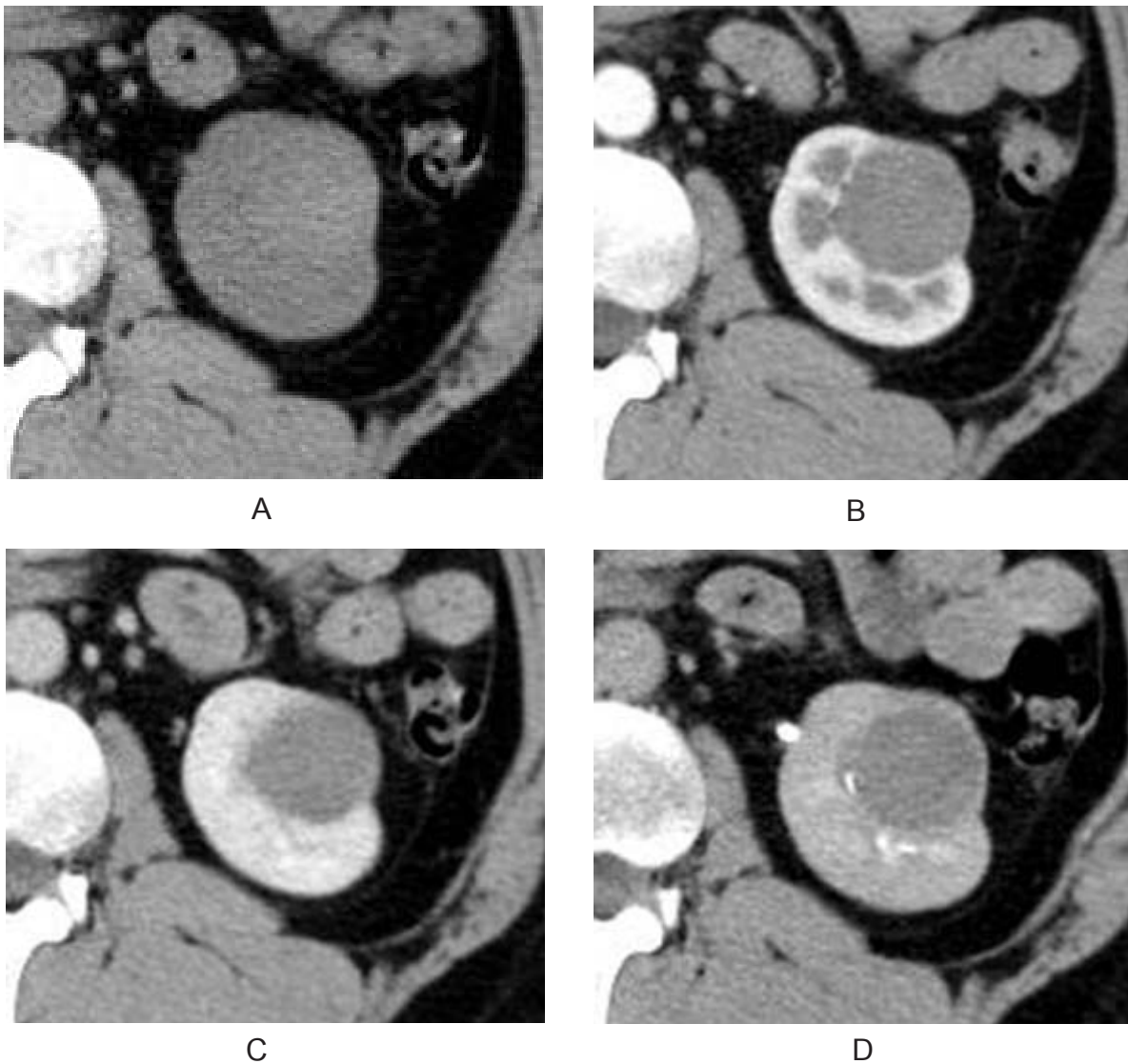


Figure 4. A 37-year-old male with no known underlying disease. CT scan in unenhanced image (A.) shows a 3.3-cm hyperdense lesion with Hounsfield unit (HU) of 49 at the lower pole of left kidney (HU of the adjacent renal cortex = 35). After contrast media administration, this lesion shows no significant enhancement with HU of 51 in corticomedullary phase (B.), HU of 53 in nephrographic phase (C.) and HU of 48 in excretory phase (D.). No solid component, calcification or septation is seen. This lesion was classified as Bosniak IIF. He underwent left partial nephrectomy about 13 days after receiving CT scan and pathologically proven of papillary renal cell carcinoma.

Discussion

Bosniak classification system is widely accepted by radiologists and urologists as a useful management guideline of cystic renal masses. Nowadays, there are many studies about Bosniak lesions which are shown to have variations in the

outcomes such as rates of progression in complexity and malignancy rates. In the study of Andrew D. Smith *et al.*,⁽⁶⁾ they found that 25% of resected Bosniak IIF lesions and 54% of resected Bosniak III lesions were malignancy. In the study of Graumann O, *et al.*⁽⁵⁾ who reviewed published studies of complex renal cysts

and found that malignancy rates in Bosniak II, IIF and III groups were 12%, 12% and 61%, respectively. In our study, due to limitation of retrospective study design and small patient numbers which can underestimate malignancy rate and only shows one lesion in Bosniak category IIF (6.7%) that was malignancy and none of those lesions in Bosniak category II and III were proved malignant. In this case was a 37-year-old healthy male with incidental finding of solid renal mass from ultrasound screening in case microscopic hematuria in other hospital and was refer to our hospital for further surgery and received pre-operative CT scan. The final histopathological report showed a 3 x 2 x 1.5-cm renal cell carcinoma, papillary subtype (type I). Typically, papillary renal cell carcinoma is hyperdense and homogeneous enhancement at CT.⁽⁶⁾ Through MRI, papillary renal cell carcinoma is typically hypointense on T2-weighted images, perhaps because of the iron-containing hemosiderin which is sometimes found in the cytoplasm of the tumor cells.⁽⁷⁾ However, a papillary renal cell carcinoma can occasionally manifest as a cystic mass, possible due to inherent architecture or secondary to cystic degeneration and extensive necrosis.⁽⁸⁾ In addition, some papillary RCC are known to be enhanced only minimally after intravenous contrast material administration which may have been mistaken for cystic lesions at the time of image interpretation, especially if near-water attenuation was measured on precontrast CT images.^(6,9) There are still certain limitations for the diagnosis of this group of tumor.

Other limitation of this study is due to we used follow up imaging of these cystic lesions and no

pathological prove in all lesions which should be standard diagnosis of malignancy of these renal cysts. However, we used follow-up imaging more than 2 years to prove that should be benign lesions.^(10,11) And other limitation is due to the different imaging techniques of follow up study which can cause difference Bosniak category due to limitation in some imaging techniques, however MRI usually upgrade category from CT scan and ultrasound also widely accepted to be standard method of follow up Bosniak category II cysts.^(10,11)

Conclusion

In conclusion, 6.7% (1 of 15) of resected Bosniak IIF lesion was malignancy in this study which was papillary renal cell carcinoma. None of Bosniak II and III lesions have been proved malignant. Approximately, 3% (4 of 144) of Bosniak II lesions had progression in complexity and reclassification as Bosniak IIF and III lesions with the average time to progression about 1,358 days (range, 477 – 1,904). All of these progressed lesions were managed by imaging surveillance without surgical resection. None of the patients with Bosniak IIF and III lesions had progression in complexity. However, a small number of lesions in these Bosniak IIF and III groups were detected. When compared to the chance of complexity progression of Bosniak II group, the chance of progression of complexity in these 2 groups still exist.

However, several limitations in this study as described above and there are still have chance of malignancy and progression of complexity of these groups of renal cysts. Follow-up imaging should be considered especially in Bosniak category IIF.

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