

Analysis of predictive factors for the  
malignancy in Bosniak category IIF  
renal cysts

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malignancy in Bosniak category IIF  
renal cysts

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This certifies that the Master's Thesis of  
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## ABSTRACT

### **Analysis of predictive factors for the malignancy in Bosniak category IIF renal cysts**

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**Purpose:** To evaluate the clinical features associated with malignancy in category IIF renal cysts and to determine the optimal length of follow-up for them.

**Materials and Methods:** Radiological and clinical informations were retrospectively searched for Bosniak IIF lesions in computed tomographic (CT) reports from January 1996 to January 2011. 78 adult patients with unenhanced and contrast material-enhanced CT results and with lesions either surgically resected or with 1 year or more of surveillance were included. Renal cyst progression to category III in follow-up studies was defined as an increase in complexity of cyst. I monitored radiologic changes and progression of renal cysts during the follow-up period, and analyzed the pathologic results of those patients who were treated surgically.

**Results:** 21 patients without radiological progression underwent the operation on their own account and of 57 patients under surveillance, five patients (8.8%) showed evidence of progression to category III, with a median time to progression of 9 months (6-26). There was no significant difference in age,



gender, cyst size, change in cyst size, multiple septa, wall thickness, calcification, or hyperdensity between the progressive and non-progressive group. Of five patients with radiologic progression, three patients underwent the operation; two patients (66.7%) showed malignancy, whereas of 21 patients without radiological progression underwent the operation; four patients (19.0%) showed malignancy. All six patients reported as malignancy were pT1 renal cell carcinomas and showed no recurrence during postoperative median follow-up of 20 months (4-35). Of 24 patients who underwent the operation, the malignant group showed a significantly older age than the benign group ( $p=0.035$ ), but the hyperdensity was the sole significant predictive factor for malignancy (OR 13.000, 95% CI 1.201 to 140.734;  $p=0.035$ ).

**Conclusions:** It is hard to decide the optimal length of follow-up for Bosniak IIF lesions because of variable time to progression, but those with hyperdensity would need more close surveillance because of high risk of malignancy.

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Key words: kidney, cyst, renal cell carcinoma, computed tomography

# **Analysis of predictive factors for the malignancy in Bosniak category IIF renal cysts**

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## **I. INTRODUCTION**

Renal cysts are common lesions; more than 50% of the population in the age of 50 years or older have renal cysts <sup>1</sup>, and most of simple renal cysts do not need further evaluation or intervention as they are harmless <sup>2</sup>. Due to the advances and the widespread of abdominal ultrasonography, abdominal computed tomography (CT), and magnetic resonance imaging (MRI) for diagnostic tool <sup>3</sup>, the incidence of complex renal cysts and cystic renal cell carcinoma has increased in recent years. Advanced imaging studies have brought early diagnosis and early treatment as a result. However, they have also brought unnecessary surgeries and following post-operative complications for benign renal cysts. Therefore, it is very important to differentiate cystic renal cell carcinoma from benign renal cysts during the pre-operative work-up <sup>3</sup>. Abdominal CT or MRI studies are used to differentiate between simple renal cysts from cystic renal malignancies. But it is still a major challenge to recognize difference between them.

Bosniak suggested a classification system for complex renal cysts in 1986 <sup>4</sup>, and his classification system is the one that is most widely used to evaluate renal cysts <sup>2</sup>. Cysts are classified into four different levels for patient

management: simple renal cysts (category I), benign renal cysts with complications but not in need of surgery (category II), potentially malignant renal cysts in need of surgery (category III), and cystic renal cell carcinomas (category IV) <sup>3</sup>. However, the controversy and difficulty lies in those complex cystic renal masses that lie between category II and III <sup>2, 5</sup>. To address this problem and based on the clinical experience of Bosniak, the IIF categorization was suggested first in 1993 for lesions that are more complex than a category II cyst but still thought to be benign and require only serial imaging to confirm stability <sup>6, 7</sup>.

Presently, there is a consensus that radiologic surveillance and intervention upon increasing complexity are safe and effective to manage category IIF lesions <sup>8</sup>, but optimal length of follow-up for these lesions still remain unproven. Moreover, clinical features associated with malignancy in category IIF lesions have not been defined although it has been suggested that there is a wide range of complexity in category IIF lesions: those that are minimal category IIF with minimal findings that are very likely benign and those that are more closer to category III in complexity. Therefore, I retrospectively evaluated the pathological and clinical outcomes of category IIF lesions to evaluate the clinical features associated with malignancy in category IIF lesions and to determine the optimal length of follow-up for them based on the single institute experience.

## II. MATERIALS AND METHODS

After receiving institutional review board approval at Severance Hospital, patients were identified retrospectively from a urology billing database using diagnosis codes for renal cysts, renal masses, renal neoplasms, as well as from a preexisting radiology database using the key words ‘Bosniak’ and ‘cyst’ from January 1996 to January 2011. A total of 5,946 patients were diagnosed with cystic renal disease. Among them, 279 patients were diagnosed category IIF by CT imaging. Patients 18 years and older with unenhanced and contrast material-enhanced CT results and with lesions either surgically resected or with 1 year or more of follow-up were included. An experienced single uro-radiologist reviewed all of them and only 78 patients with cysts confirmed to be category IIF by him were included in the study. Clinical characteristics of all patients are shown in Table 1.

**Table 1.** Patients’ characteristics

Variables	Data
No. of patients	78
Age (year)*	62 (27–85)
Sex (Male:Female)	59:19

\*Values are expressed as median (range).

The images were obtained preoperatively using multislice 64 detector row helical CT scanner (Lightspeed, GE Medical System, Milwaukee, WI, USA). In abdominal pelvic contrast CT protocol, after unenhanced images were acquired, arterial phase and delay phase scanning were performed. In kidney spiral CT protocol, CT images were obtained in the precontrast phase, corticomedullary

phase (30-45 seconds after contrast injection), nephrographic phase (85-120 seconds after contrast injection), and excretory phase.

Upon chart review follow-up radiologic and pathologic data were recorded. The radiologic data were surveyed for date of radiologic study, change in lesion size, interval change in complexity. The existence of radiological factors including multiple septa, wall thickening, calcification, and hyperdensity were determined and cyst progression to category III was defined as an increase in cyst complexity diagnosed by the radiologist, but an increase in cyst size was not considered progression.

Clinical differences between the radiological progressive group and non-progressive group were compared. Patients underwent the operation in the case of progression to category III or on their own account although they did not have progression. Their pathological outcomes were recorded, including benign or malignant histology, histological subtype and pathological stage. Marsupialization was included in the procedure for those non-progressive group who gets surgery. Fluid cytology and cyst wall were tested by marsupialization to tell whether they are benign or malignant.

To analyze the differences between radiological progressive group and non-progressive group, Mann-Whitney U test were used for continuous variables, and Fisher exact test for categorical variables. And to analyze the differences between benign group and malignant group, Mann-Whitney U test or Fisher exact test were also used. In addition, to identify the predictive factors for malignant group, a univariate binary logistic regression analysis was conducted. A p-value less than 0.05 was considered statistically significant. SAS ver. 9.2 (SAS Institute Inc., Cay, NC, USA) software was used for the statistical analysis.

### **III. RESULTS**

Of 78 patients with category IIF lesions, 21 patients underwent the operation on their own account although they did not have progression. Of 57 patients under surveillance, five (8.8%) cases showed renal cyst progression with the median time to progression of 9 months (6-26), whereas 52 patients (91.2%) showed radiological stability during the median follow-up period of 25.5 months (12-96).

There were no significant differences in age ( $p=0.707$ ), sex ( $p>0.999$ ), cyst size ( $p=0.737$ ), size change ( $p=0.139$ ), multiple septa ( $p>0.999$ ), wall thickening ( $p=0.587$ ), calcification ( $p=0.067$ ) or hyperdensity ( $p>0.999$ ) between the progressive group and non-progressive group in 57 patients under surveillance (Table 2).

**Table 2.** Comparison between progressive and non-progressive groups in 57 patients under surveillance

Variables	Progression (N=5)	Non-progression (N=52)	p-value
Age (year) *	60.2 (41–80)	64.5 (39–85)	0.707
Sex			>0.999
Male	4 (80%)	42 (81%)	
Female	1 (20%)	10 (19%)	
Cyst size (cm) *	2.6 (1.5–3.2)	2.1 (0.6–9.8)	0.737
Size change			0.139
No change	4 (80%)	32 (62%)	
Increase	0 (0%)	17 (33%)	
Decrease	1 (20%)	3 (5%)	
Multiple septa			>0.999
Yes	4 (80%)	43 (83%)	
No	1 (20%)	9 (17%)	
Wall thickening			0.587
Yes	2 (40%)	12 (23%)	
No	3 (60%)	40 (77%)	
Calcification			0.067
Yes	0 (0%)	24 (46%)	
No	5 (100%)	28 (54%)	
Hyperdensity			>0.999
Yes	1 (20%)	13 (25%)	
No	4 (80%)	39 (75%)	

\*Values are expressed as median (range).

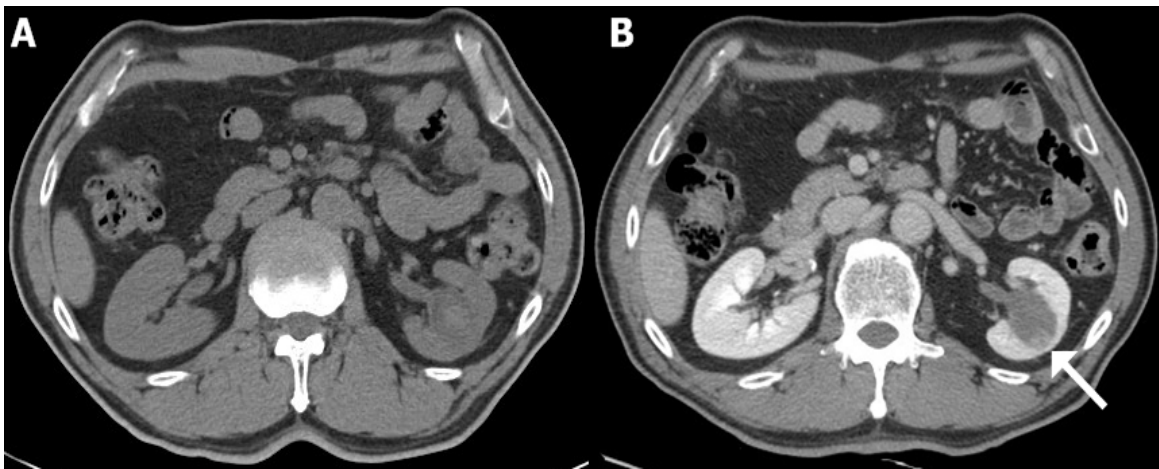
Among 5 patients with radiologic progression, three patients underwent the operation; two patients (66.7%) were found to be malignant. Of 21 patients without radiological progression underwent the operation; four patients (19.0%) showed malignancy. All six patients reported as malignancy were pT1 renal cell carcinomas and showed no recurrence during postoperative median follow-up of 20 months (4-35) (Table 3).

**Table 3.** Pathologic outcomes of the patients who underwent the operation

Variables	Progression (N=5)	Without progression (N=21)
No. of operation	3	21
No. of malignant tumor	2 (66.7%)	4 (19.0%)
Pathologic T stage		
T1a	2	3
T1b	0	1
Histologic type		
Clear	1	3
Papillary	1	1
Fuhrman's grade		
I	0	4
III	2	0



Of 24 patients who underwent the operation, there were no significant differences in sex, size, size change, multiple septa, wall thickening, calcification, or hyperdensity ( $p=0.621$ ,  $0.194$ ,  $0.801$ ,  $>0.999$ ,  $0.129$ ,  $0.052$ , and  $0.050$ , respectively), whereas the malignant groups showed a significantly older age compared to that of the benign group ( $p=0.035$ ) (Table 4). However, based on the univariate logistic regression analysis, the hyperdensity was the sole significant predictive factor for malignancy (OR 13.000, 95% CI 1.201 to 140.734;  $p=0.035$ ) (Fig. 1) (Table 5).



**Fig. 1.** Computed tomographic findings of IIF renal cysts with hyperdensity (A) A 68-year-old man with a category IIF cystic lesion in the left kidney. Pre-contrast axial CT scan depicts a 3.2-cm hyperdensity cystic mass. (B) On follow-up 9 months later, Contrast-enhanced CT scan shows measurable enhancement (arrow). Based on these findings, the lesion was reclassified as category III cysts. Radical nephrectomy was performed, and pathologic examination revealed a renal cell carcinoma.

**Table 4.** Comparison between benign and malignant groups in 24 patients who underwent the operation

Variables	Benign (N=18)	Malignant (N=6)	p-value
Age (year) *	56.5 (27–69)	64 (39–73)	0.035
Sex			0.621
Male	11 (61%)	5 (81%)	
Female	7 (39%)	1 (19%)	
Cyst size (cm)*	3.9 (1.4–13.0)	3.1 (1.5–4.7)	0.194
Size change			0.801
No change	15 (83%)	5 (83%)	
Increase	1 (6%)	0 (0%)	
Decrease	2 (11%)	1 (17%)	
Multiple septa			>0.999
Yes	14 (76%)	5 (83%)	
No	4 (24%)	1 (17%)	
Wall thickening			0.129
Yes	4 (24%)	4 (67%)	
No	14 (76%)	2 (33%)	
Calcification			0.052
Yes	9 (50%)	0 (0%)	
No	9 (50%)	6 (100%)	
Hyperdensity			0.050
Yes	5 (29%)	5 (83%)	
No	13 (80%)	1 (17%)	

\*Values are expressed as median (range).

**Table 5.** Univariate logistic regression analysis evaluating the predictive factors for malignancy in 24 patients who underwent the operation

Variables	p-value	Odds ratio	95% CI
Age	0.098	1.100	0.983-1.232
Sex			
Male	0.334	3.182	0.304-33.259
Female	-	Reference	Reference
Cyst size	0.155	0.667	0.381-1.166
Size change			
No change	-	Reference	Reference
Increase	0.971	0.939	0.033-26.648
Decrease	0.760	1.500	0.111-20.299
Multiple septa			
Yes	0.772	1.429	0.127-16.026
No	-	Reference	Reference
Wall thickening			
Yes	0.060	7.000	0.920-53.232
No	-	Reference	Reference
Calcification			
Yes	0.095	0.077	0.004-1.567
No	-	Reference	Reference
Hyperdensity			
Yes	0.035	13.000	1.201-140.734
No	-	Reference	Reference

#### IV. DISCUSSION

The Bosniak classification system is used to diagnose and manage complex renal cysts. If the category IIF designation of the Bosniak classification system is accurate, it is predictable to minimize progression in category IIF and low malignancy rate <sup>8</sup>. In this study, five (8.8%) cases showed radiological progression with the median time to progression of 9 months (6-26). This is lower than the 14.8% progression rate in 81 cysts in the O'Malley et al series <sup>8</sup>, and the 13% progression rate in 69 cysts in the Smith et al series <sup>10</sup>, but higher than the 4.8% in 48 cysts in the Israel and Bosniak series <sup>9</sup>. And 21 cases without progression were treated surgically in this study. Four cases (19%) showed malignancy, 17 cases showed benign cysts. The malignant rate in surgically treated category IIF lesions is historically 0% to 25% but the previous studies reporting these values were done in a small population <sup>10, 11</sup>. This supports the clinical impact of Bosniak IIF category. The malignant rate in surgically treated category III lesions is historically 25% to 100% <sup>8</sup>. If all historically reported category III lesions with pathologically proven diagnosis are summed, there is an overall 51% malignant rate <sup>12</sup>. In this study, three of 5 cases of progression were treated surgically except for the two cases that refused surgery; 2 (66.7%) of these 3 cysts were found to be malignancy. The proportion of malignant rate in this study is higher than that of historically reported malignant rate. This further also supports the clinical impact of Bosniak IIF category.

In this study, the malignant group showed a significantly older age than the benign group ( $p=0.035$ ), but the age was not the significant predictive factor for malignancy (OR 1.100, 95% CI 0.983 to 1.232;  $p=0.098$ ). Several mechanism exist by which renal cysts may become hyperdense. Proposed mechanisms by which cysts have elevated CT attenuation include hemorrhage with clot retraction, concentration of the protein components of blood, elevation of iron

content, colloid formation, infection, and transient iodine accumulation within a simple cyst<sup>13</sup>. Renal masses having densities greater than 40 Hounsfield units (HU) are considered “solid” and are usually malignant<sup>14</sup>. Complicated renal cysts with hyperdensity have slightly higher attenuation (15 to 40 HU) than simple cysts<sup>13</sup>. However these hyperdense renal cysts could not be easily differentiated from a solid renal tumor. The results of this study showed that hyperdensity was associated with renal cell carcinoma in category IIF lesions (OR 13.000, 95% CI 1.201 to 140.734; p=0.035). Almost malignant cases have hyperdensity. The hyperdensity was important and there was an increased possibility of getting a malignant result in surgically treatment as the hyperdensity was many. This suggest that hyperdensity could generate a masking effect in diagnose malignancy. These hyperdensity cystic tumors may have been mistaken for benign cystic lesions at the time of image interpretation. However additional studies with an increased number of patients are necessary to determine these predictive factors definitively.

No clear guidelines concerning the proper radiologic follow-up duration and interval have been proposed, but if increasing complexity is found by continuous radiologic studies, exploratory surgery is recommend to rule out malignancy<sup>8</sup>. Most category IIF patients are not surgically treated. Therefore, additional follow-up studies are needed to confirm that the cysts in these patients remain stable and benign. To address this problem and based on the clinical experience of Bosniak duration of follow-up was suggested first in 2012. There is a wide range of complexity in category IIF lesions: those that are minimal category IIF with minimal findings that are very likely benign and close to category II in complexity, the lesions may necessitate only 1-2 year follow-up. Whereas those that are more worrisome and closer to category III in complexity, the lesions may need to be followed up for a longer period (eg. 3-4 years or longer)<sup>15</sup>. In my study, the median time to progression was 9 (6-26) months. The longest time to progression observed 26 months. The patient with

longest time to progression was 80 years old and his physical condition was not good. So the patient refused surgery. The results of this study make it predictable for follow-up studies of at least 2 years. This is because renal cyst show slow growth pattern<sup>9</sup>. The time to progression varied, therefore, further multi-center studies with longer follow-up periods and a greater number of patients are needed to determine the proper duration of follow-up for category IIF lesions.

It can be argued that Category IIF cysts should be surgically removed, for example, in young patients who do not want more follow-up studies<sup>9</sup>. However, surgery is not necessary for all patients. In my study, the malignant rate of surgically treated category IIF lesions was 19%. And most of malignant cases in surgically treated progressive groups are low stage renal cell carcinoma. Its prognosis is satisfactory compared to other renal malignancies due to low metastatic rate<sup>16-19</sup>. Therefore, delayed diagnosis of several malignancies did not have severe consequences or adversely affect patients' outcome. So for the elderly patients in poor physical condition, follow-up study is recommended rather than surgery. And for the young patients, too frequent follow-up study would be unnecessary.

This study had a few limitations. Because study was retrospective and the cases were collected over 10 years, the radiologic studies were performed on a variety of helical and conventional CT scanners. In addition, the type and amount of intravenous contrast material also varied. Second, intervention was influenced by clinical parameters such as patient age and physical condition. Although the Bosniak classification system is based on imaging findings, it can add variability to managing cases by affecting clinical parameters. Lastly, the sample size was small because some patients moved away or transferred to another hospital, resulting in follow-up loss. Additional patients and a prolonged follow-up period are needed in future studies.

## **V. CONCLUSION**

It is hard to decide the optimal length of follow-up for Bosniak IIF lesions because of variable time to progression. Especially, those with hyperdensity would need more close surveillance because of high risk of malignancy. However, too frequent follow-up study in elderly patients would be unnecessary considering that most of malignant cases are low stage.

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**ABSTRACT (IN KOREAN)**

**Bosniak category IIF 복합 신낭종에서의 악성을 예측할수 있는  
인자들에 대한 연구분석**

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황 종 호

**목적:** Bosniak IIF 복합 신낭종에서 악성을 예측하는 임상적인  
요인들을 확인하고, 적절한 추적검사 기간을 정하고자 한다.

**재료 및 방법:** 1996년 1월부터 2011년 1월까지 전산화 단층촬영 (CT)  
에서 Bosniak IIF 로 보고 된 병변의 영상의학적, 임상적인 특징을  
후향적으로 조사하였다. CT 에서 조영 증강이 되거나 되지 않은  
경우를 포함하였고, 수술을 받았거나, 1년 이상의 추적관찰이 된 성인  
78명의 환자를 대상으로 하였다. Category III 로 신낭종의 진행은 추적  
영상검사에서 복잡성의 증가가 있는 경우로 정의하였다.  
추적관찰기간 동안 영상 소견의 변화 및 신낭종의 진행 정도를  
확인하였고, 수술한 경우의 병리결과를 분석하였다.

**결과:** 21례는 영상의학적으로 진행을 하지 않았지만 수술을 위해  
수술을 받았다. 추적관찰을 한 57례중, 5례 (8.8%)에서 신낭종이  
category III 로 진행하였고, 진행한 시점은 median 9개월 (6-26) 이었다.

추적관찰 기간동안 진행을 한 군과 하지 않은 군간에 나이, 성별, 낭종의 크기, 낭종의 크기 변화, 다발성 격막, 두꺼운 내벽, 석회화, hyperdensity 소견에서 통계적으로 유의한 차이는 없었다. 영상의학적으로 진행한 5례 중 3례에서 수술을 받았고 그 중 2례 (66.7%) 에서 악성으로 판별되었다. 반면 영상의학적으로 진행을 하지 않았지만 수술을 받은 21례 중 4례 (19.0%) 에서 악성으로 판별되었다. 악성으로 판별된 총 6례 모두 pT1 stage 의 신세포암으로 진단되었고, 수술 후 median 20개월 (4-35) 의 추적관찰기간 동안 재발 소견은 관찰되지 않았다. 수술을 받은 총 24례중 악성으로 판별된 환자 군은 양성으로 판별된 환자 군에 비해 나이가 유의하게 많았으나 ( $p=0.035$ ), hyperdensity 소견만이 악성을 예측할 수 있는 유일한 인자로 나타났다 (OR 13.000, 95% CI 1.201 to 140.734;  $p=0.035$ ).

**결론:** 진행한 시점이 다양하여 Bosniak IIF 신낭종의 적절한 추적관찰 기간을 결정하는 데에는 어려움이 있다. 하지만 hyperdensity 소견을 가진 경우 악성의 위험성이 있어 더욱 세심한 추적관찰이 필요함을 알 수 있었다.

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핵심되는 말: 신장, 낭종, 신세포암, 전산화 단층촬영