

The Histopathologic Correlation of Bosniak 3 Cyst Subclassification



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OBJECTIVE	To evaluate the histopathologic correlation of recently described subclassification of Bosniak category 3 cysts (3s and 3n).
MATERIALS AND METHODS	A total of 106 patients who underwent partial/radical nephrectomy due to a complex renal cyst (\geq Bosniak 3) were retrospectively reviewed. All the scans of the patients were reevaluated by 2 experienced urologists. Bosniak 3 cysts were reclassified as 3n (nodularity on the cyst wall/septae) and 3s (septated cysts without nodularity) as described in a recently published paper. Group 1 consisted of patients with Bosniak 3s, Group 2 consisted of patients with Bosniak 3n, and Group 3 consisted of patients with Bosniak 4 cysts. Three groups were compared according to patients' characteristics, radiological findings, histopathologic results, and survival outcomes.
RESULTS	There were 52 patients in Bosniak 3 group and 54 patients in Bosniak 4 group. Mean follow-up was 35.3 months. Among Bosniak 3 cysts, 37 lesions were classified in 3s and 15 were classified in 3n. Malignancy was higher in 3n group than 3s (86.7% vs 54.1%, $P = .026$). Lesion size was significantly lower for malignant cysts compared to benign ones in the patients with Bosniak 3 lesions (44.2 ± 27.5 vs 80 ± 55.9 $P = .005$). In the subgroups, malignant lesions were significantly smaller than benign lesions in 3s group similar to general Bosniak 3 group. Most of the Bosniak 3 lesions were organ confined and low grade.
CONCLUSION	The subclassification of Bosniak 3 cysts as 3s and 3n can help to differentiate highly suspicious malignant lesions from the relatively less suspicious ones. UROLOGY 129: 126–131, 2019. © 2019 Elsevier Inc.

Renal cell carcinomas (RCC) can present as cystic lesions in up to 7% of cases.^{1,2} Cystic lesions are classified according to the Bosniak classification.³ The original classification was created in 1986 based on computed tomography (CT), later modifications were introduced in 1993 including Bosniak 2F to bridge Bosniak 2 and 3. Bosniak 1 and 2 cysts are accepted as benign lesions that do not require further follow-up. Bosniak 4 lesions are mostly malignant and no doubt most of them undergo surgery. The challenging issue is Bosniak 2F and 3 cysts for clinicians. The malignancy rate is <1% in stable type 2F cysts during follow-up. Nearly 20% of type 2F cysts are reclassified as type 3-4 during follow-up and

malignancy rate rises to 85% in these patients.⁴ In a recent review, the malignancy risk of Bosniak 3 cysts was reported as 51% and this means that 49% of the patients are overtreated with surgery.⁴ This overtreatment rate, together with excellent cancer-specific survival, raised the question of whether surveillance can be an alternative in these patients. In a recent trial, Bosniak 3 cysts were subclassified as septate enhancing Bosniak cysts (3s) and cysts with wall or septation-only nodularity (3n) to differentiate the patients appropriate for surveillance.⁵ This was a surveillance study and only 27% of the patients underwent surgery, progression was reported according imaging rather than histopathologic examination. We aimed to evaluate the histopathologic correlation of the subclasses of Bosniak category 3 cysts (3s and 3n) to determine patients with lower malignancy risk and define potential candidates for active surveillance.

MATERIALS AND METHODS

After ethical approval from the local ethics committee, 633 patients who underwent radical or partial nephrectomy between January 2010 and December 2018 due to a renal mass in a tertiary center were retrospectively evaluated. The exclusion criteria were as follows: patients with noncystic lesions, previous

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renal surgery or renal cyst treatment, lesions <category 3 Bosniak cysts, missed histologic or radiological data, and multiple complex cysts. In our clinic, in accordance with the current guidelines' recommendations, all Bosniak 3 and Bosniak 4 cysts are surgically removed, none of the patients was followed up. The imaging data were gathered from our electronic imaging database system. The most recent contrast-enhancing abdominal CT or magnetic resonance imaging (MRI) images within the last 3 months before surgery were reviewed by 2 experienced urologists. Radiologists were blinded for both the final histopathologic diagnosis and previous assessment of imaging. Cystic lesions were grouped according to Bosniak classification by urologists. Controversial lesions according to the urologists were included in the higher category as suggested by Israel and Bosniak.⁶ Bosniak 3 cysts were reclassified as 3n (nodularity on the cyst wall/septae) and 3s (septate cysts without nodularity), as previously described by Pruthi et al⁵ (Fig. 1).

Patient characteristics, radiological and histopathologic findings were recorded. Then the study group was divided into 3 groups according to preoperative Bosniak classification. Group 1 consisted of patients with Bosniak 3s, Group 2 consisted of patients with Bosniak 3n, and finally Group 3 consisted of patients with Bosniak 4 cysts. The 3 groups were compared according to patient characteristics, radiological findings, histopathologic results, and survival outcomes.

Surgical procedure was performed as open or laparoscopic partial/radical nephrectomy depending on the location and size of tumor, patient characteristics, and experience of the surgeon. For follow-up, at the end of the sixth month, patients with low-risk tumor underwent ultrasonography, while patients with intermediate- or high-risk tumors underwent abdominal computed tomography. Then all patients were followed with abdominal CT annually.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, IL) software program. Mann-Whitney *U* test and chi-square test were used between Groups 1 and 2, Kruskal Wallis test and chi-square test were used between Groups 1, 2, and 3. In addition, Mann-Whitney *U* test and chi-square test were used for subgroup analysis of Bosniak 3 cysts according to malignancy and tumor diameter. Data

are given as mean \pm SD. However, results of analysis are given as median data. Statistical significance was defined as $P < .05$.

RESULTS

Data of 633 patients who underwent partial or radical nephrectomy were evaluated. Among the patients, 109 patients had renal cystic lesions. Patients who had <Bosniak 3 cysts were excluded. Finally, 106 patients who had complex renal cysts (\geq Bosniak 3) were included in the study. The mean age was 56.9 ± 13.5 years (27-84) and 67.9% of patients were male. Patient characteristics are given in Table 1. There were 52 patients in Bosniak 3 group and 54 patients in Bosniak 4 group. Among Bosniak 3 cysts, 37/52 (71.2%) were classified as 3s and 15/52 (28.8%) were as 3n. In histopathologic examination, 25 and 81 of all patients had benign and malign lesions, respectively. Most of the tumors were confined to the kidney in both the Bosniak 3s and 3n groups, whereas only 1 patient had extracapsular invasion in the 3s group. Also, nearly all tumors were graded as Fuhrman grade 1-2; only 1 lesion in 3s was graded Fuhrman 3. There was no local recurrence and mortality during mean 35.3 months' follow-up in the Bosniak 3 group.

Comparison of patient characteristics according to Bosniak classification is given in Table 2. Age was found to be lower in the Bosniak 3s groups compared to 3n (52.1 vs 59.5 , $P = .047$). Although tumor diameter was similar, malignancy was higher in the 3n group than 3s (86.7% vs 54.1% , $P = .026$). Malignancy rates of the cysts according to Bosniak classification are given in Figure 2. The endophytic-exophytic localization of tumors was not different in the 2 groups. In malignant lesions of the Bosniak 3 groups, all of malignant lesions were cRCC and pRCC in 3n. However, there were 10% chRCC and 15% mcRCC in the 3s group ($P = .606$).

Lesion size was significantly lower for malignant cysts compared to benign ones in patients with Bosniak 3 lesions (44.2 ± 27.5 vs 80 ± 55.9 $P = .005$). In the subgroups, malignant lesions were significantly smaller than benign lesions in group 3s similar to general 3 group (43.3 ± 30.2 vs 81.2 ± 58.5 $P = .011$), whereas in Bosniak 3n and 4 lesions, malignant and benign lesion sizes were not significantly different.

For Bosniak 4 lesions, malignancy rate was found to be 88.9%, and 41.6% of them were high-grade tumors (Fuhrman grade 3-4). Local recurrence developed in 4 patients in Bosniak 4 group. Finally, overall mortality and tumor-specific mortality were 18.5% and 7.4%, respectively.

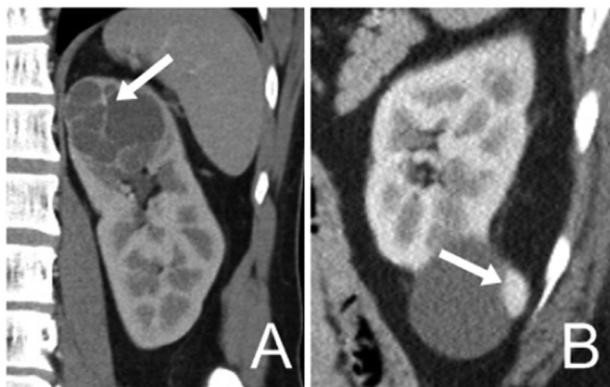


Figure 1. Subclassified Bosniak 3 renal cysts in contrast-enhancing abdominal computed tomography. (A) Bosniak 3s cyst with enhanced multiple septations (arrows). (B) Bosniak 3n cyst with nodularity (arrows) on the cyst wall.

COMMENT

Management of Bosniak category 3 lesions is still under debate. Nearly half of these patients are overtreated with surgery. Differentiation of higher malignancy risk lesions from lower ones is very important for preoperative counselling of patients and also allows us to use active surveillance more safely.

Needle biopsy of renal cystic lesions is a challenging issue.⁷ The question is whether the result can be trusted if it is negative. The other major problem is the possible change in the character of cystic fluid contents as a result of hemorrhage due to biopsy. This can make it hard to assess further imaging during follow-up. Thus, biopsy has a limited role in cystic renal lesions and therapeutic decisions are mainly made according to radiological findings.

Table 1. Patients' characteristics

Data			Values (n = 106)
Age (y), mean ± SD (range)			56.9 ± 13.5 (27-84)
Follow-up (mo), mean ± SD (range)			35.3 ± 25.1 (1-101)
Gender, n (%)	Male		72 (67.9)
	Female		34 (32.1)
Hypertension, n (%)	Yes		28 (26.4)
Imaging method, n (%)	CT		43 (40.6)
	MRI		32 (30.2)
	CT + MRI		31 (29.2)
Tumor side, n (%)	Right		53 (50)
	Left		53 (50)
Tumor diameter (mm), mean ± SD (range)			63 ± 41.6 (16-230)
Operation type, n (%)	OPN		35 (33)
	ORN		59 (55.7)
	LPN		5 (4.7)
	LRN		7 (6.6)
Tumor location, n (%)	Endophytic		24 (22.6)
	Exophytic		82 (77.4)
Bosniak cyst classification, n (%)	Type 3	3s	37 (34.9)
	(n = 52)	3n	15 (14.2)
	Type 4		54 (50.9)
Histopathologic type, n (%)	Benign		25 (23.6)
	Malign	cRCC	59 (72.8)
	(n = 81)	pRCC	14 (17.2)
		chRCC	4 (4.5)
		mcRCC	4 (4.5)
Pathologic T stage, n = 81 (%)	T1a		34 (42)
	T1b		23 (28.4)
	T2a		8 (9.9)
	T2b		4 (4.9)
	T3a		11 (13.6)
	T3b		1 (1.2)
Fuhrman grade, n (%)	Grade 1-2		60 (74.1)
	Grade 3-4		21 (25.9)
Surgical margin positivity, n (%)			2 (2.5)
Local recurrence, n (%)			4 (4.9)
Mortality, n (%)			10 (9.4)
Tumor specific mortality, n (%)			4 (3.8)

chRCC, chromophobe renal cell carcinoma; cRCC, clear cell-renal cell carcinoma; CT, computed tomography; LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radical nephrectomy; mcRCC, multi cystic renal cell carcinoma; MRI, magnetic resonance imaging; OPN, open partial nephrectomy; ORN, open radical nephrectomy; pRCC, papillary renal cell carcinoma.

The original Bosniak classification was based on CT images.³ The imaging techniques have evolved over the years and new imaging modalities were introduced for the evaluation of renal cystic lesions including contrast-enhanced ultrasound. Recent studies suggest that the diagnostic value of CT and MRI is limited in cystic renal lesions, and contrast-enhanced ultrasound may improve the diagnostic accuracy in these patients.⁸ The limitation of the imaging studies in this field is the lack of histopathologic correlation of all lesions included in the study.

RCC with cystic component have a better long-term prognosis compared to solid ones. Donin et al reported that RCC with cystic architecture had lower rates of local recurrence and metastases compared to solid tumors regardless of size.⁹ Although half of them are benign and malignant ones have excellent prognosis, total nephrectomy and kidney loss is not rare for Bosniak 3 lesions. In a study by Weibl et al, total nephrectomy was performed in 17 cases

out of 54 patients (31%) with Bosniak 3 lesions.¹⁰ In the present study among 52 patients with Bosniak 3 lesions, 33 had malignancy and none of them had local recurrence or metastases during follow-up. Also, nearly all Bosniak 3 tumors were organ confined and had low Fuhrman grade in the histologic examination.

Bosniak category 3 cysts are considered to be a heterogeneous group because of their complex radiological features. In Bosniak 3 lesions, nodularity can be seen as part of septae or cyst wall and can be distinguished easily from Bosniak 4 lesions which have solid mass with a large cystic or necrotic component.⁵

In a follow-up study, 140 lesions in 111 patients that were all Bosniak ≥2F were evaluated.⁵ Bosniak 3 lesions were subclassified into 3s and 3n according to enhancing thickened wall/septal nodularity (3n) or only enhancing septations (3s). This subclassification was made to aid prediction of patients to undergo surgery or to continue

Table 2. Comparison of the groups according to the Bosniak classification

Data	Bosniak 3 (n = 52)			Bosniak 4 (n = 54)	P [†]
	3s (n = 37)	3n (n = 15)	P*		
Age (y), mean ± SD (range)	52.1 ± 13.6 (27-78)	59.5 ± 10.5 (32-71)	0.047	59.5 ± 13.6 (31-84)	.031
Follow-up (months), mean ± SD (range)	38.8 ± 26.8 (1-97)	42.5 ± 21.1 (1-94)	0.686	30.9 ± 24.5 (2-101)	.192
Gender, n (%)			0.158		.306
	Male	22 (59.5)	12 (80)	38 (70.4)	
	Female	15 (40.5)	3 (20)	16 (29.6)	
Hypertension, n (%)	Yes	7 (18.9)	5 (33.3)	16 (29.6)	.422
Tumor side, n (%)	Right	18 (48.6)	9 (60)	26 (48.1)	.616
	Left	19 (51.4)	6 (40)	28 (51.9)	
Tumor diameter (mm), mean ± SD (range)		60.7 ± 48.7 (16-230)	48.9 ± 25.5 (20-109)	68.5 ± 39.5 (28-204)	.041
Tumor location, n (%)	Endophytic	8 (21.6)	3 (20)	13 (24.1)	.930
	Exophytic	29 (78.4)	12 (80)	41 (75.9)	
Malignancy, n (%)	Benign (n = 25)	17 (45.9)	2 (13.3)	6 (11.1)	<.001
	Malignant (n = 81)	20 (54.1)	13 (86.7)	48 (88.9)	
Histopathologic type (n = 81), n (%)	cRCC	13 (65)	9 (69.2)	37 (77.1)	
	pRCC	2 (10)	4 (30.8)	8 (16.7)	.037
	chRCC	2 (10)	0 (0)	2 (4.2)	
	mcRCC	3 (15)	0 (0)	1 (2.1)	
Pathologic T stage (n = 81), n (%)	T1a	13 (65)	7 (53.8)	14 (29.2)	
	T1b	4 (20)	5 (38.5)	14 (29.2)	.002
	T2a	2 (10)	1 (7.7)	5 (10.4)	
	T2b	0 (0)	0 (0)	4 (8.3)	
	T3a	1 (5)	0 (0)	10 (20.8)	
	T3b	0 (0)	0 (0)	1 (2.1)	
Fuhrman grade (n = 81), n (%)	Grade 1-2	19 (95)	13 (100)	28 (58.3)	<.001
	Grade 3-4	1 (5)	0 (0)	20 (41.6)	
Surgical margin positivity, n (%)		1 (2.7)	0 (0)	1 (1.9)	.810
Local recurrence, n (%)		0 (0)	0 (0)	4 (7.4)	.062
Overall mortality, n (%)		0 (0)	0 (0)	10 (18.5)	.001
Tumor-specific mortality, n (%)		0 (0)	0 (0)	4 (7.4)	.004

cRCC, clear cell-renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; mcRCC, multicystic renal cell carcinoma; pRCC, papillary renal cell carcinoma.

* Mann-Whitney *U* test and chi-square test were used between type 3s and type 3n groups of Bosniak type 3 cysts groups.

† Kruskal Wallis test and chi-square test were used between Bosniak 3s, Bosniak 3n, and Bosniak 4 cysts groups.

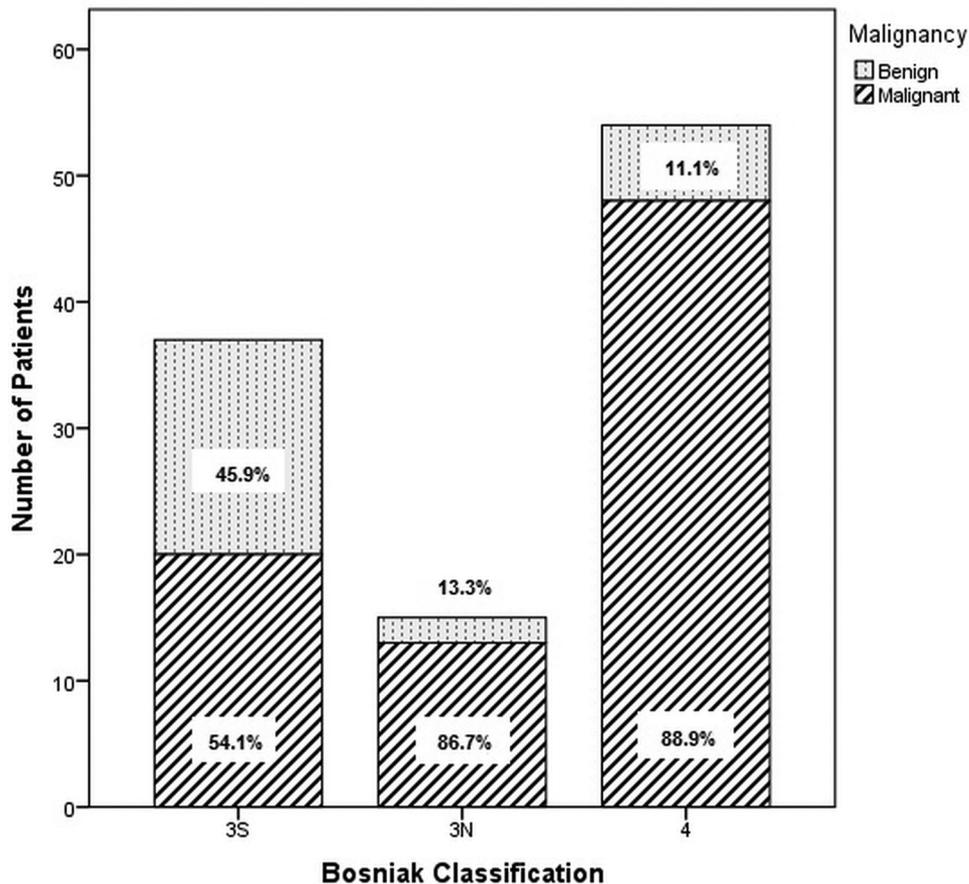


Figure 2. Malignancy rates of the cysts according to the subclassification.

active surveillance. Only 30 (27%) of the patients underwent surgery in the former study. The authors concluded that subclassification of Bosniak 3 cysts may better characterize their clinical behavior.

Active surveillance is used based on the oncological characteristics of a malignancy. If the chance of progression and metastasis is low for a tumor, the postponement of treatment or in some instances avoiding unnecessary treatment may significantly contribute to the patient's quality of life. Bosniak 3 cystic lesions are candidates for active surveillance because of higher rates of benign pathology and excellent prognosis if malignant. In the present study, we found that malignancy rates for 3n and 4 cysts were 86.7% and 88.9%, respectively ($P = .812$). However, it was 54.1% for 3s cysts ($P < .05$). This finding shows that 3n cysts are more aggressive and behave like Bosniak 4 cysts; however, 3s cysts are more indolent. According to the findings in our study, we think that active surveillance is much more convenient for type 3s cysts and that type 3n cysts are candidates for surgery.

In a study with limited number of patients, Lam et al reported that smaller lesions (<4 cm) are more likely to be malignant compared to larger ones.¹¹ Nouhaud et al did not find any correlation between lesion size and malignancy risk in a group of patients including Bosniak 2F, 3, and 4 cysts.¹² Our findings are coherent with Lam et al in that the malignant Bosniak 3 lesions were smaller in size. Additionally, we

found that malignant lesions were also significantly smaller than benign lesions in 3s, whereas no statistically significant difference found in Bosniak 3n and 4 lesions.

The most common surgical pathology of malignant lesions in Bosniak 3 cysts are clear cell RCC, papillary RCC, and chromophobe RCC.^{9,13} It was also reported that Bosniak 3 tumors almost always have low Fuhrman grade.¹⁴ In concordance with the previous studies, the most common histologic subtype was clear cell carcinoma followed by papillary, chromophobe, and multicystic RCC, and nearly all tumors in Bosniak 3 cysts had low Fuhrman grade in our study. The distribution of subtypes was not different in Bosniak 3s and 3n groups.

Limitations of this study include its retrospective design and lack of standardized imaging during last 8 years. Contrast-enhanced ultrasonography was not performed in our institution and we cannot correlate our pathologic findings with it. The strengths of our study are pathologic correlation of all radiological findings and examination of images by 2 blinded experienced urologists to avoid potential bias.

CONCLUSION

The subclassification of Bosniak 3 cysts as 3s and 3n can help to differentiate highly suspicious malignant lesions from the relatively less suspicious ones. We found that

nearly half of 3s lesions are benign, whereas 3n cysts behave like Bosniak category 4 and are nearly 90% malignant. Further studies would clarify the prognostic factors for Bosniak 3 cysts and the issue to propose a change in the Bosniak Classification to include Bosniak 3s and 3n subgroups.

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