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Predictive Value of Additional Clinical and Radiological Parameters for Discrimination of Malignancy in Bosniak 3 Cysts

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Keywords
Bosniak classification · Renal cyst · Kidney cancer · Malignancy

Abstract
Introduction: Almost half of the cystic renal lesions are still overdiagnosed and overtreated. New clinical and radiological parameters are needed to distinguish the malignant Bosniak 3 lesions from the benign ones. We aimed to evaluate the clinical and radiological parameters that may be related to malignancy risk for Bosniak category 3 renal cysts. ***Materials and Methods:*** Patients who underwent surgical resection of a histopathologically confirmed Bosniak 3 renal cyst between March 2007 and September 2019 were evaluated. Two experienced uro-radiologists have reevaluated the last preoperative computed tomography and/or MRI images of the patients and reclassified the lesions according to the Bosniak classification. They also reported cystic features such as nodularity, septation, focal thickening, enhancement, and calcification. Clinical, pathological, and oncological outcomes were recorded. Then patients were divided into 2 groups as Group 1 (benign pathology) and Group 2 (malignant pathology) according to final histopathological report. ***Results:*** A total of 79 patients were included in this study. Mean follow-up time was 47 ± 34 months. There were 30 patients in Group 1 and 49 patients in Group 2. Hypertension ($p = 0.001$) and smoking history ($p = 0.008$) were more common in malignant group. Among the radiological findings, lower tumor diameter ($p = 0.024$), presence of cyst wall enhancement ($p = 0.025$), presence of nodularity ($p = 0.002$), and presence of focal thickening ($p = 0.031$) were found to be statistically significant for malignancy. Most of the tumors were at pathological T1 stage and Fuhrmann Grade 1–2. Only nodularity was found to be independent predictive factor for malignancy in multivariate analysis. ***Conclusion:*** Clinical factors including hypertension and smoking, radiological factors including lower lesion size, cyst wall enhancement, nodularity, and focal thickening were predictors for malignancy of Bosniak 3 cysts.

Introduction

The Bosniak classification is mainly based on contrast-enhanced computed tomography (CCT) images. The classification has been used widely for almost 30

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years and is considered the most effective method for identifying cystic renal masses. However, the management of cystic renal masses still remains challenging for clinicians. Despite all the diagnostic methods, almost half of the cystic renal lesions are still overdiagnosed and overtreated. Nowadays, active surveillance is a popular option for Bosniak 3 lesions. Active surveillance is 1st introduced in the European Association of Urology (EAU) guidelines in 2019 and recommended for cautiously selected patients [1]. Treating Bosniak 3 cysts, like renal cell carcinoma (RCC), results in about 49% overtreatment [2]. New clinical and radiological parameters are needed to distinguish the malignant Bosniak 3 lesions from the benign ones. For this purpose, studies investigating the importance of lesion size, nodularity, and cyst ratio have been published recently [3–5]. The Bosniak classification is an important method to predict malignancy rather than a comprehensive management algorithm that applies to the biological behavior of lesions, such as aggressiveness which affects the patient's prognosis. Medical factors such as age, comorbidity, life expectancy, and preference for treatment should all be considered. It is uncertain whether the risk factors for RCC, such as smoking, hypertension, and metabolic syndrome, can be useful for discrimination of malignancy from benign cases of cystic renal lesions. In the present study, we aimed to study the known and possible clinical and radiological parameters that may be related to malignancy risk to discriminate malignant lesions from benign ones for Bosniak category 3 renal cysts.

Materials and Methods

In this study, 823 patients who underwent surgical resection of a renal mass between March 2007 and September 2019 were retrospectively evaluated. This study protocol was approved by the institutional review board (approval number: 2019/06).

Two experienced uro-radiologists reevaluated the last preoperative CT and/or MRI images of patients with histopathologically confirmed cystic renal mass. They were blind to final pathology, preoperative imaging reports, and also each other. The radiologists reclassified the cystic lesions according to the Bosniak classification. They also reported cystic features such as nodularity, septation, focal thickening, enhancement, and calcification. If a lesion was assigned to different Bosniak categories by 2 radiologists, it was assigned to the upper Bosniak category [6]. After radiological assessment, patients with lesions other than Bosniak category 3 were excluded. In addition, patients with previous renal surgery, patients with incomplete imaging or histopathological reports, and patients with previous diagnostic or therapeutic interventions for renal cysts were excluded from the study. In line with current guidelines, there were no patients with Bosniak 3 lesions in the follow-up protocol. All patients with Bosniak 3 lesions were treated with surgery. Radiological images were obtained from the institutional electronic database.

Clinical, pathological, and oncological outcomes of the patients were recorded. Then all patients were divided into 2 groups as Group 1 (patients with benign pathology) and Group 2 (patients with malignant pathology) according to final histopathological report. The type of the surgery was chosen according to the surgeons' preference with taking into consideration partial indexes, cyst localization, diameter, and patient characteristics. Preoperative and postoperative 3rd month Cr levels were recorded. ΔCr was described as the difference between the postoperative 3rd month Cr and preoperative Cr levels.

Statistical Analysis

Data were analyzed for univariate and multivariate analysis using the Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, IL, USA) software program. In univariate analysis, Mann-Whitney U test and χ^2 test were performed for comparison of clinical, radiological, and pathological findings between Groups 1 and 2. Statistical significance was defined as $p < 0.05$. In multivariate analysis, linear regression model was created, and significant factors after univariate analysis were evaluated by the model for detecting the predictive values of the factors. Median value was used while performing analyses. Data were given as mean ± SD.

Results

A total of 79 patients with histopathologically confirmed Bosniak 3 cyst were included in this study. Thirty patients with benign pathology were included in Group 1, and 49 patients with malignant pathology were included in Group 2. Benign pathological lesions included benign multilocular cysts and multilocular cystic renal cell neoplasm of low malignant potential. Malignant pathological lesions included clear cell RCC, papillary RCC, and chromophobe RCC. Mean follow-up time was 47 ± 34 months, and mean age of all patients was 57.4 ± 13.8 years. Clinical and radiological findings of the groups are given in Table 1. No difference was found between the groups in terms of age, gender, BMI, and presence of metabolic syndrome. Hypertension ($p = 0.001$) and smoking history ($p = 0.008$) were more common in the malignant group. Among the radiological findings, lower tumor diameter ($p = 0.024$), presence of cyst wall enhancement ($p = 0.025$), presence of nodularity ($p = 0.002$), and presence of focal thickening ($p = 0.031$) were found to be statistically significant for malignancy.

The number of patients who underwent radical nephrectomy was 16 (53.3%) and 19 (38.8%) in Group 1 and Group 2, respectively ($p = 0.206$). Preoperative Cr was 0.88 ± 0.19 (0.6–1.38) mg/dL for Group 1 and 0.93 ± 0.2 (0.55–1.59) mg/dL for Group 2 ($p = 0.178$). Postoperative Cr was 1.09 ± 0.33 (0.6–2.1) mg/dL for Group 1 and

Table 1. Comparison of the patients' characteristics, clinical, and radiological findings of the benign and malign groups of Bosniak 3 cysts

Variable	Bosniak 3 cysts (n = 79)		
	group 1 (benign n = 30)	group 2 (malignant n = 49)	p value
Age, years, mean ± SD (range)	55.4±14.7 (27–79)	58.6±13.2 (31–87)	0.368
Follow-up, months, mean ± SD (range)	44.1±27.1 (3–96)	48.8±37.7 (1–143)	0.912
Gender, n (%)			
Male	16 (53.3)	33 (67.3)	0.213
Female	14 (46.7)	16 (32.7)	
BMI, kg/m^2, mean±SD (range)	29.2±5.4 (24–41)	27.9±3.9 (17–34)	0.917
Hypertension, n (%)	6 (20)	27 (55.1)	**0.001**
Metabolic syndrome, n (%)	5 (16.7)	11 (22.4)	0.474
Smoking history, n (%)	4 (25)	17 (68)	**0.008**
Tumor side, n (%)			
Right	19 (63.3)	26 (53.1)	0.533
Left	11 (36.7)	23 (46.9)	
Radiologic tumor diameter, mm, mean ± SD (range)	66.9±48.2 (21–230)	48±33 (16–160)	**0.024**
Presence of septation, n (%)	28 (93.3)	43 (87.8)	0.349
Septation thickness, mm, mean ± SD (range)	1.8±1 (1–5)	2.1±1.3 (0.1–6)	0.5
Septation enhancement, n (%)	21 (70)	42 (85.7)	0.092
Cyst wall thickness, mm, mean ± SD (range)	1.8±1 (1–11)	1.7±1.6 (1–10)	0.849
Presence of cyst wall enhancement, n (%)	21 (70)	44 (89.8)	**0.025**
Presence of multilocular cyst, n (%)	23 (76.7)	38 (77.6)	0.939
Nodularity, n (%)	3 (10)	21 (42.9)	**0.002**
Nodule diameter, mm, mean ± SD (range)	1.3±0.8 (0.7–2.2)	1.5±0.7 (0.5–3.5)	0.661
Focal thickening, n (%)	4 (13.3)	17 (34.7)	**0.031**
Presence of calcification, n (%)	5 (16.7)	4 (8.2)	0.213
Tumor location, n (%)			
Endophytic	7 (23.3)	12 (24.4)	0.907
Exophytic	23 (76.7)	37 (75.6)	

SD, standard deviation Mann-Whitney U test and χ^2 test were used between benign and malign groups of Bosniak type 3 cysts.

1.09 ± 0.47 (0.55–3.56) mg/dL for Group 2 (p = 0.750). ΔCr levels were 0.21 ± 0.26 (−0.2 to 0.9) for Group 1 and 0.16 ± 0.34 (−0.29 to 1.97) for Group 2 (p = 0.206). For the patients who underwent radical and partial nephrectomy, ΔCr levels were 0.36 ± 0.39 (−0.29 to 1.97) and 0.05 ± 0.14 (−0.21 to 0.4), respectively (p < 0.001). Both in Groups 1 and 2, ΔCr levels were higher in patients with radical nephrectomy compared with the patients with partial nephrectomy (p < 0.001 for Group 1 and p = 0.016 for Group 2).

Postoperative histopathological and oncological results for the groups are given in Table 2. The most common histopathological type in the malignant group was clear cell RCC (71.4%). Most of the tumors were at pathological T1 stage (87.7%) and Fuhrmann Grade 1–2 (89.8%). One patient (3.3%) in Group 1 and 1 patient (2%) in Group 2 were died due to cardiac morbidities. Only one patient (2%) was died because of renal cancer. After the creation of the linear regression model, only nodularity was found to be an independent predictive factor for malignancy (p = 0.004, HR: 0.442; 95% CI: +0.152 to +0.732). Multivariate analysis results are given in Table 3.

Discussion

Classification of renal cystic masses was completed by Bosniak [7] in 1986. Although this classification has undergone some modifications [8], there is still controversy about Bosniak category 3 renal cysts. Nearly half of lesions are malignant among Bosniak category 3 renal cysts.

Table 2. Postoperative pathologic and oncologic results of the benign and malign groups of Bosniak 3 cysts

Variable	Group 1 (n = 30)	Group 2 (n = 49)	p value
Histopathologic type (n = 49), n (%)			
ccRCC	–	35 (71.4)	–
pRCC		10 (20.4)	
chRCC		4 (8.2)	
Pathologic T stage (n = 49), n (%)			
T1a	–	28 (57.1)	–
T1b		15 (30.6)	
T2a		3 (6.1)	
T2b		2 (4.1)	
T3a		1 (2)	
T3b		0 (0)	
Fuhrmann grade (n = 47), n (%)			
Grade 1–2	–	44 (89.8)	–
Grade 3–4		3 (6.1)	
Surgical margin positivity, n (%)	–	3 (6.1)	–
Local recurrence, n (%)	0 (0)	2 (4.1)	0.262
Overall mortality, n (%)	1 (3.3)	2 (4.1)	0.866
Tumor specific mortality, n (%)	0 (0)	1 (2)	0.692

ccRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; chRCC, chromophobe renal cell carcinoma. Mann-Whitney U test and χ^2 test were used between benign and malign groups of Bosniak type 3 cysts.

Table 3. Multivariate analysis results of the significant factors predicting malignancy in Bosniak 3 cysts

Variables (model p = 0.004)	p value	HR	CI
Hypertension	0.564	0.087	−0.217/+0.392
Smoking history	0.071	0.259	−0.023/+0.541
Radiologic tumor diameter, mm	0.226	−0.002	−0.006/+0.002
Cyst wall enhancement	0.992	0.182	−0.191/+0.555
Nodularity	**0.004**	**0.442**	**+0.152/+0.732**
Presence of focally thickening	0.776	−0.048	−0.392/+0.295

Regression analysis was used for determination of the predictive factors to malignancy in Bosniak type 3 cysts. HU, Hounsfield unit.

To recommend a surgery that may result in total organ loss with only 50% chance of malignancy is a somewhat hard circumstance for both clinician and patient. Other than radiological features, there are some known risk factors for RCC like hypertension, obesity, and smoking. Moreover, in recent years some articles examined radiological features other than known Bosniak definitions to further stratify the patients about the risk of malignancy in Bosniak category 3 lesions. One of the most important articles in this field was published by Pruthi et al. [5] and proposed the division of category 3 into 2 as 3 s and 3 n according to the presence of nodularity. This was an active surveillance study and they concluded that 3 s cysts were more likely to regress and 3 n cysts were more likely to progress. We conducted a similar study to review our clinical results retrospectively and found similar results to this former study (malignancy risk 54.1% for 3 s and 86.7% for 3 n) [9]. In the present study, presence of nodularity was also found to be statistically significant for malignancy.

Total organ loss is not a rare entity during surgery for Bosniak category 3 renal lesions. In a recent study, it was reported that only 69% of patients with Bosniak 3 cysts could be managed by partial nephrectomy and 31% underwent radical nephrectomy [10]. In that study, no data were attained about renal functions of patients that had undergone radical nephrectomy. In our study, radical nephrectomy was performed for 44% of patients with Bosniak 3 cysts, and this rate was higher in the benign subgroup (53.3 vs. 38.8%). The difference in radical nephrectomy rates may be attributed to mean tumor size, which is evidently higher in our study group, and unfavorable partial nephrectomy indexes. Also, the ΔCr levels were significantly higher in the radical nephrectomy group which shows negative impairment of total renal functions.

In the present study, we aimed to study the known and possible parameters that may be related to malignancy risk to further stratify the risk of malignancy for Bosniak category 3 renal lesions. Cigarette smoking, obesity, and hypertension are established causal risk factors for RCC [11]. In univariate analysis, we showed that smoking and hypertension are significantly associated with risk of malignancy in Bosniak category 3 cysts.

There are only a few studies investigating the specific radiological features of complex cysts beyond Bosniak classification to discriminate malignant lesions from benign ones. In these studies, enhancement of the septa, presence of nodular component, nodular enhancement, and nodule-to-cyst ratio were mostly found to be associated with likelihood of malignancy [12–14]. We studied extensive radiological parameters that could be useful for discrimination of malignant lesions (Table 1). Of these, radiological tumor diameter, presence of cyst wall enhancement, presence of nodularity, and focal thickening were found to be associated with malignancy in our study group.

Active surveillance has become an option for cystic renal masses in recent years. In a recent study, Erkkilä et al.

[15] showed that active surveillance for renal masses increased from 8 to 23% between 2006 and 2016. Although it is not routinely recommended, there are several ongoing and published studies about this topic [3–5, 16, 17]. In one of these studies by Shaish et al. [4], during a median of 2.7 years follow-up, 45% of <4 cm Bosniak 3 and 4 lesions were downgraded. The authors concluded that especially <2 cm lesion size can be a consideration for active surveillance. The lesion size was found to be lower in patients with malignant pathology in the current study.

The ideal solution for the improvement of diagnostic accuracy in Bosniak category 3 cysts is to create a nomogram that includes Bosniak classification characteristics, known risk factors about patient characteristics, and radiological features other than Bosniak classification. We could not create such a nomogram because of the limited number of patients. We believe that testing of a nomogram like this could be valuable in the future during a high volume multicenter trial.

Several studies are ongoing about biomarkers and oncometabolites in RCC for early diagnosis and assessment of prognosis [18]. In the future, we believe that with inclusion of these biomarkers in primary evaluation of cystic renal lesions, in addition to radiological characteristics and clinical features, diagnostic accuracy will be improved in the Bosniak category 3 lesions.

The limitations of the current study include the retrospective design, lack of standardized imaging method, and relatively limited number of patients. And also our data do not include the patients who had Bosniak 3 cyst and followed up with active surveillance.

Conclusion

The Bosniak classification alone is not enough to assess the malignancy risk in category 3 cysts. For proper preoperative patient counseling and accurate decision-making, clinical and radiological parameters should be taken into consideration for assessment of malignancy risk in addition to the Bosniak classification. In this study, clinical factors including hypertension and smoking and radiological factors including lower lesion size, cyst wall enhancement, nodularity, and focal thickening were predictors of malignancy.

Statement of Ethics

This study protocol was approved by the local Ethics Committee (approval number: 2019/06).

Conflict of Interest Statement

All the authors declare no conflicts of interest.

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Author Contributions

Ertugrul Sefik: study concept and design, data extraction, drafted the manuscript, and critical revision of the manuscript. Ibrahim Halil Bozkurt: study concept and design, data extraction, and drafted the manuscript. Gulsen Yucel Oguzdogan: data extraction, review of the images, data analysis, and data interpretation. Serdar Celik: data extraction, data analysis, and data interpretation. Ismail Basmaci: data extraction, data interpretation, and writing the manuscript. Sacit Nuri Gorgel: data extraction, data interpretation, and writing the manuscript. Erhan Aydin: data extraction, data analysis, and data interpretation. Zehra Hilal Adibelli: study concept and design, and review of the images. Enver Vardar: review of the histopathological reports and critical review of the manuscript. Bulent Gunlusoy: critical review of manuscript, and data analysis. Tansu Degirmenci: study concept and design, data extraction, and drafted the manuscript.

References

1 Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, et al. European association of urology guidelines on renal cell carcinoma: the 2019 update. Eur Urol. 2019 May;75(5):799–810.
2 Schoots IG, Zaccai K, Hunink MG, Verhagen PCMS. Bosniak classification for cmplex renal cyts reevaluated: a systematic review. J Urol. 2017;198:12–21.
3 Kashan M, Ghanaat M, Hötker AM, Duzgol C, Sanchez A, DiNatale RG, et al. Cystic renal cell carcinoma: a report on outcomes of surgery and active surveillance in patients retrospectively identified on pretreatment imaging. J Urol. 2018 Aug;200(2):275–82.
4 Shaish H, Ahmed F, Schreiber J, Hindman NM. Active surveillance of small (<4 cm) Bosniak category 2F, 3, and 4 renal lesions: what happens on imaging follow-up? AJR Am J Roentgenol. 2019;212(6):1215–22.
5 Pruthi DK, Liu Q, Kirkpatrick IDC, Gelfond J, Drachenberg DE. Long-term surveillance of complex cystic renal masses and heterogeneity of bosniak 3 lesions. J Urol. 2018;200(6):1192–9.
6 Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. Urology. 2005;66(3):484.
7 Bosniak MA. The current radiological approach to renal cysts. Radiology. 1986;158(1):1–10.

8 Silverman SG, Pedrosa I, Ellis JH, Hindman NM, Schieda N, Smith AD, et al. Bosniak classification of cystic renal masses, version 2019: an update proposal and needs assessment. Radiology. 2019;292(2):475–88.
9 Sefik E, Bozkurt IH, Adibelli ZH, Aydin ME, Celik S, Oguzdogan GY, et al. The histopathologic correlation of Bosniak 3 cyst subclassification. Urology. 2019 July;129:126–31.
10 Weibl P, Hora M, Kollarik B, Shariat SF, Klatte T. Management, pathology and outcomes of Bosniak category IIF and III cystic renal lesions. World J Urol. 2015;33(3):295.
11 McLaughlin JK, Lipworth L, Tarone RE. Epidemiologic aspects of renal cell carcinoma. Semin Oncol. 2006 Oct;33(5):527–33.
12 Reese AC, Johnson PT, Gorin MA, Pierorazio PM, Allaf ME, Fishman EK, et al. Pathological characteristics and radiographic correlates of complex renal cysts. Urol Oncol. 2014 Oct;32(7):1010–6.
13 Benjaminov O, Atri M, O'Malley M, Lobo K, Tomlinson G. Enhancing component on CT to predict malignancy in cystic renal masses and interobserver agreement of different CT features. AJR Am J Roentgenol. 2006;186(3):665–72.
14 Song C, Min GE, Song K, Kim JK, Hong B, Kim CS, et al. Differential diagnosis of complex cystic renal mass using multiphase computerized tomography. J Urol. 2009 Jun;181(6):2446–50.
15 Erkkilä K, Tornberg SV, Järvinen P, Järvinen R, Kilpeläinen TP, Visapää H, et al. Evolving clinical picture of renal cell carcinoma: a population-based study from Helsinki. Urol Int. 2019;102(4):390–8.
16 Lam CJ, Kapoor A. The true malignancy risk of Bosniak III cystic renal lesions: active surveillance or surgical resection? Can Urol Assoc J. 2018;12(6):E276–80.
17 Smith AD, Carson JD, Sirous R, Sanyal R, Remer EM, Allen BC, et al. Active surveillance versus nephron-sparing surgery for a Bosniak IIF or III renal cyst: a cost-effectiveness analysis. AJR Am J Roentgenol. 2019 Apr;212(4):830–8.
18 Yong C, Stewart GD, Frezza C. Oncometabolites in renal cancer. Nat Rev Nephrol. 2020 Mar;16(3):156–72.