Using Contrast-Enhanced Ultrasound in Addition to Cross-Sectional Imaging for Indeterminate Renal Cysts May Lead to Overclassification in Bosniak III Category: A Case-Control Study

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Keywords

Bosniak classification · Complex renal cysts · Contrast-enhanced ultrasound · Malignancy · Imaging modalities

Abstract

Introduction: Indeterminate renal cysts may require several imaging modalities before clinical decision. The aim of this study was to investigate the effect of the imaging modality used to characterize indeterminate renal cysts on the pathological findings after surgical resection. **Methods:** From our institutional database, we identified all patients surgically treated for Bosniak III renal masses between January 2008 and January 2018. All complex renal cysts were characterized with a combination of computed tomography (CT) and/or magnetic resonance imaging (MRI), and/or contrast-enhanced ultrasound (CEUS) and discussed during a multidisciplinary tumor board. Potential association between clinical/radiological characteristics and the pathological findings were investigated, using univariate and multivariate analyses. **Results:** Of the 52 renal cystic lesions surgically removed, with a preoperative diagnosis of Bosniak III renal cyst, 19 (37%) were malignant and 33 (63%) were benign. The proportion of malignant lesions decreased from 47% when the

renal cyst was characterized with cross-sectional imaging (CT and/or MRI) to 17% when the diagnosis required CEUS in addition to cross-sectional imaging. In multivariate analysis, prior history of renal cell carcinoma was associated with a higher risk of malignancy ($p = 0.016$) and diagnosis made with CEUS was associated with a lower risk of malignancy ($p = 0.040$). **Conclusion:** We found that using CEUS in addition to cross-sectional imaging to characterize indeterminate renal cysts tends to redefine Bosniak III as lesions with a lower risk of malignancy and can lead to overclassification.

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Introduction

Renal cell carcinoma (RCC) represents 2–3% of all cancers, with the highest incidence in Western countries [1]. Over the last 2 decades, the incidence of RCC has increased by about 2%, mainly due to increased incidental detection of tumors by ultrasound and computed tomography (CT) [2]. Along with solid renal tumors, there has also been an increase in the detection of cystic renal masses, of which 8–15% are complex cystic masses [3].

Table 1. Characteristics of the population

Variables	N = 52
Median age at diagnosis, years [IQR]	54.1 [46.0; 61.7]
Gender, <i>n</i> (%)	
Male	28 (54)
Female	24 (46)
Smoking status, <i>n</i> (%)	
Active/former	15 (33)
Never	31 (67)
Median BMI, kg/m ² [IQR]	25.3 [22.1; 26.6]
End-stage CKD, <i>n</i> (%)	5 (10)
Prior history of RCC, <i>n</i> (%)	7 (13)
Symptoms at diagnosis, <i>n</i> (%)	11 (21)
Median size of the lesion, cm [IQR]	4.5 [3.0; 6.9]
Imaging modality that allowed the classification of the cyst, <i>n</i> (%)	
Cross-sectional imaging	34 (65)
CEUS	18 (35)
Type of surgery, <i>n</i> (%)	
Partial nephrectomy	43 (83)
Radical nephrectomy	9 (17)
Pathology	
Benign, <i>n</i> (%)	33 (63)
Epithelial cyst	21
Cystic nephroma	11
Metanephric adenoma	1
Malignant, <i>n</i> (%)	19 (37)
Multilocular cystic RCC	9
Clear cell RCC	3
Papillary RCC	3
Tubulocystic RCC	2
Chromophobe RCC	2

IQR, inter-quartile range; BMI, body-mass index; CKD, chronic kidney disease; RCC, renal cell carcinoma; CEUS, contrast-enhanced ultrasound.

Since the introduction of the Bosniak classification for renal cysts in 1986, clinical management of such lesions has been primarily guided by radiological assessment [4]. While simple and minimally complex cysts (Bosniak I and II) do not require any treatment or surveillance, more complex cysts (Bosniak III and IV) are recommended for treatment due to a high risk of malignancy [5, 6].

However, the imaging characterization has improved over time and could lead to stage migration. The Bosniak classification was extended to magnetic resonance imaging (MRI) in 2004 [7] and updated in 2019 [8]. Contrast-enhanced ultrasound (CEUS) is now a valuable alternative to further characterize indeterminate renal lesions [9, 10]. Consequently, we aimed to investigate the effect of CEUS for the characterization of indeterminate renal cysts on CT and/or MRI before surgical resection.

Materials and Methods

Population of the Study

After approval from the Ethical Committee of the French Association of Urology, a retrospective review was performed to identify patients with Bosniak III renal cyst treated surgically at our center between January 2008 and January 2018. Patients who underwent active surveillance or watchful waiting because of elder age and comorbid disease were excluded. We also excluded patients with a known hereditary syndrome or when a Bosniak III cyst was associated with a synchronous solid renal tumor. Out of 926 patients treated with radical or partial nephrectomy for renal tumors, we identified 52 patients diagnosed with a preoperative Bosniak III lesion who met our criteria for analysis. Demographic and medical characteristics were collected. All surgical specimens were reviewed by a dedicated uropathologist (V.V.) and classified according to the 2012 International Society of Urological Pathology classification [11].

Diagnostic Imaging Studies

Prior to surgery, all imaging studies were reviewed by senior radiologists specialized in renal tumors (C.D. and J.-M.C.). The lesions were characterized by a combination of enhanced CT and/or MRI. Cysts were considered indeterminate when cross-sectional imaging was not able to distinguish between complex cysts (Bosniak III), recommended for surgical treatment, and minimally complex cysts (Bosniak IIF) that should undergo surveillance. In such cases, CEUS was ordered to better characterize the lesion and help the decision-making process. Details on imaging modalities are available in online suppl. material (for all online suppl. material, see www.karger.com/doi/10.1159/000517405).

Statistical Analysis

To test statistical significance of differences between clinical and demographic variables, we utilized χ^2 or Fisher tests for categorical variables and Wilcoxon or Kruskal-Wallis tests for continuous variables. Predictive factors of malignancy were tested in univariate analysis, with *p* value <0.05 considered to be significant. Factors with a significant *p* value in univariate analysis were tested in multivariate analysis through a logistic regression model. Statistical analysis was performed using R v.3.4.3 (<https://cran.r-project.org>).

Results

Of the 52 renal cystic lesions surgically removed with a preoperative diagnosis of Bosniak III renal cyst, 19 (37%) were malignant, and 33 (63%) were benign. Median size of the lesion was 4.5 cm (range 1.5–13 cm). Surgical pathological findings for the malignant lesions were: multilocular cystic RCC (9/19), clear cell RCC (3/19), papillary RCC (2 type 1 and 1 type 2), tubulocystic RCC (2/19), and chromophobe RCC (2/19). Only 3/19 malignant lesions were aggressive variants (2 papillary RCC and 1 clear cell RCC were International Society of Urological Pathology grade 3), while 16/19 were of low ma-

Table 2. Comparison of the clinical characteristics between benign and malignant Bosniak III renal cysts

Variables	Benign, N = 33	Malignant, N = 19	<i>p</i> value
Median age at diagnosis, year [IQR]	56.3 [47.8; 60.0]	49.1 [44.4; 63.1]	0.740
Gender, <i>n</i> (%)			
Male	16 (48.5)	12 (63.2)	0.463
Female	17 (51.5)	7 (36.8)	
Smoking status, <i>n</i> (%)			
Never	20 (69.0)	11 (64.7)	1.000
Active/former	9 (31.0)	6 (35.3)	
Median BMI, kg/m ² [IQR]	25.4 [22.5; 26.6]	25.1 [22.0; 26.2]	0.652
End-stage CKD, <i>n</i> (%)			
No	29 (87.9)	18 (94.7)	0.641
Yes	4 (12.1)	1 (5.26)	
Prior history of RCC, <i>n</i> (%)			
No	32 (97.0)	13 (68.4)	0.007
Yes	1 (3.0)	6 (31.6)	
Symptoms at diagnosis, <i>n</i> (%)			
No	25 (75.8)	16 (84.2)	0.726
Yes	8 (24.2)	3 (15.8)	
Median size of the lesion, cm [IQR]	4.80 [3.00; 7.75]	3.50 [2.75; 5.50]	0.161
Imaging modality that allowed the classification of the cyst, <i>n</i> (%)			
Cross-sectional imaging	18 (54.5)	16 (84.2)	0.063
CEUS	15 (45.5)	3 (15.8)	

p values in bold are statistically significant. IQR, inter-quartile range; BMI, body-mass index; CKD, chronic kidney disease; RCC, renal cell carcinoma; CEUS, contrast-enhanced ultrasound.

lignant potential. The findings for the benign lesions were: epithelial cyst with or without atypical cells (21/33), cystic nephroma (11/33), and metanephric adenoma (1/33).

The characteristics of the population are presented in Table 1. Overall, 43/52 patients were treated with partial nephrectomy (41 open and 2 robot-assisted) and 9/52 had radical nephrectomy (8 laparoscopic and 1 open). Among the patients treated with radical nephrectomy, 5 patients had end-stage CKD, and 4 patients had a prior history of ipsilateral malignant RCC treated with partial nephrectomy.

All the imaging studies were reviewed by dedicated radiologists specialized in renal tumors and discussed during a multidisciplinary tumor board including radiologists and urologists. For 20/52 patients, only 1 imaging modality was performed (16 CT and 4 MRI); for 20/52 patients, 2 imaging modalities were performed (14 CT + MRI, 4 CT + CEUS, 2 MRI + CEUS); for 12 patients, 3 imaging modalities were performed (CT + MRI + CEUS). CEUS was used when the cyst remained indeterminate after cross-sectional imaging (CT and/or MRI). The proportion of malignant lesions decreased from 47% when

Fig. 1. Rate of benign and malignant lesions, depending on the imaging modality that allowed the classification of the renal cyst. CEUS, contrast-enhanced ultrasound.

the renal cyst was characterized with cross-sectional imaging, to 17% when diagnosis was made with CEUS (Fig. 1). Online suppl. figures show examples of CEUS cases for indeterminate lesions after CT and/or MRI.

In order to identify predictive factors of malignancy for Bosniak III renal cysts, we compared the clinical/ra-

Table 3. Univariate and multivariate analysis of predictive factors of malignancy for Bosniak III renal cysts

Variables	Univariate		Multivariate	
	OR [95% CI]	<i>p</i> value	OR [95% CI]	<i>p</i> value
Age at diagnosis	1.00 [0.95; 1.05]	0.906	–	–
Gender				
Male	1.00 (reference)			
Female	0.56 [0.17; 1.78]	0.327	–	–
Smoking status				
Never	1.00 (reference)			
Active/former	1.21 [0.32; 4.40]	0.772	–	–
BMI	0.97 [0.82; 1.15]	0.737	–	–
End-stage CKD				
No	1.00 (reference)			
Yes	0.45 [0.02; 3.55]	0.482	–	–
Prior history of RCC				
No	1.00 (reference)			
Yes	12.7 [1.84; 351]	0.007	19.3 [2.47; 447]	0.016
Symptoms at diagnosis				
No	1.00 (reference)			
Yes	0.61 [0.11; 2.53]	0.506	–	–
Size of the lesion	0.84 [0.67; 1.06]	0.146	–	–
Imaging modality that allowed the classification of the cyst				
Cross-sectional imaging	1.00 (reference)			
CEUS	0.24 [0.05; 0.90]	0.034	0.18 [0.02; 0.78]	0.040

p values in bold are statistically significant. IQR, inter-quartile range; BMI, body-mass index; CKD, chronic kidney disease; RCC, renal cell carcinoma; CEUS, contrast-enhanced ultrasound; OR, odds ratio; CI, confidence interval.

diological characteristics between benign and malignant lesions. We found that patients with a malignant lesion after surgery had more frequently a prior history of RCC (32 vs. 3%, $p = 0.007$), a smaller cyst (3.5 vs. 4.8 cm, $p = 0.161$), and were less often diagnosed with CEUS (16 vs. 84%, $p = 0.063$) (Table 2). In multivariate analysis, prior history of RCC was significantly associated with a higher risk of malignancy (OR = 19.3, 95% CI: 2.47–447, $p = 0.016$) and diagnosis made with CEUS was significantly associated with a lower risk of malignancy (OR = 0.18, 95% CI: 0.02–0.78, $p = 0.040$) (Table 3).

Discussion

In this cohort, the radio-pathological correlation for Bosniak III renal cysts found 37% of malignant lesions overall, with important differences depending on whether the lesion remain indeterminate after CT and/or MRI or not. Since 1986, the Bosniak radiographic classification has been used to guide the management of complex renal cysts, based on the risk of RCC at the time of surgery. Both

American Urological Association Guidelines and European Association of Urology Guidelines state that Bosniak cysts greater than III should be considered as RCC and be treated accordingly [5, 6]. However, the malignancy rate of Bosniak III has the highest heterogeneity among the Bosniak classification, ranging from 31 to 100% [12, 13]. In a recent meta-analysis including radiological and surgical series from 1991 to 2016, the estimated prevalence of RCC for Bosniak III renal cysts was 0.51 (95% CI: 0.44–0.58) [14]. This means that 49% of these patients have been operated on for a benign lesion. In our cohort, the rate of benign lesions was even higher (63%). This underlines the less-than-optimal grading classification within the Bosniak III category. Interestingly, the introduction of the Bosniak IIF category in 1993 to differentiate between complex cysts and minimally complex cysts [15] did not significantly affect the overall performance of the Bosniak classification; reported rates of malignancy were 0.46 before and 0.51 after the introduction of the Bosniak IIF category [14].

With an intent to better define patients at risk for malignant lesions, we performed multivariate analysis and

found that prior history of RCC was strongly associated with the risk of malignant cyst, while the use of CEUS to characterize indeterminate cystic masses after cross-sectional imaging was associated with a lower risk of malignant lesion. Prior retrospective studies proposed several models to predict the risk of malignancy with conflicting results [16, 17]. Renal cysts are frequently found in patients with end-stage CKD and have different prognostic significance depending on the clinical context. Native renal cysts and dialysis duration have been identified as risk factors of RCC in renal transplant recipients [18]. In our cohort, only 1/5 patients with a Bosniak III renal mass and a history of end-stage CKD was found to have a malignant lesion after surgery.

The most striking finding of our study is the trend toward overclassification when CEUS was used in addition to cross-sectional imaging to characterize indeterminate renal cysts. The definition of a Bosniak III lesion is based on the identification of thickened/irregular walls or septa with measurable enhancement [8]. It was initially defined for CT and was secondarily extended to MRI [7]. We used the same definition for CEUS when it was required to characterize indeterminate cystic renal masses after cross-sectional imaging [9]. Although CEUS was shown to be very concordant with CT to distinguish Bosniak II–IIF from Bosniak III–IV [19], our study is the first to highlight the role of the diagnostic strategy in the pathological outcomes. If a lesion is difficult to characterize with cross-sectional imaging and requires CEUS, the probability of having a malignant lesion is much lower than a Bosniak III lesion diagnosed with CT or MRI (17 vs. 47%). CEUS provides high sensitivity in detecting microbubble signal from the vascularized wall, septa, or solid nodules of complex cystic renal masses [9]. It has been shown that CEUS had the potential to improve lesion classification and could change therapeutic options [20]. For example, it could be useful to reclassify Bosniak IIF lesions as benign cysts, allowing it to stop the follow-up. However, as CEUS can detect only a few microbubbles traveling in thin septations with a superior time and spatial resolution compared with any other imaging modalities, it may be too sensitive, with a potential to overclassify certain cases of benign cysts as Bosniak III [21]. In our study, if CEUS was not performed, the indeterminate lesions after cross-sectional imaging would have been probably classified as Bosniak IIF with follow-up imaging at 6 months.

If a significant proportion of complex cysts are benign, it is also suspected that RCC in a complex cyst may have a different natural history and may not be as aggressive as in a solid mass [22]. A risk ratio of 0.06 to die of

clear cell RCC with a cystic architecture was reported compared to solid RCC [23]. This is consistent with the 16/19 malignant lesions with low malignant potential found in our cohort. Consequently, arguing that a significant proportion of patients are overtreated, some authors investigated the role of active surveillance in cystic renal masses as an alternative to surgical treatment. The University of Toronto described its institutional experience of cystic renal masses surveillance [3]. Out of 122 patients with Bosniak III cysts, only 37 (31%) underwent either surgical or ablative intervention, while the other patients (69%) did not receive treatment and went under the surveillance. At last follow-up, with a median time of 65 months, all patients with surveillance were alive with no metastatic progression and none of the cysts were upgraded to Bosniak IV. These results need to be validated by prospective studies. However, surveillance for Bosniak III cysts in select patients could be considered a safe alternative in order to prevent overtreatment and limit metastatic spread.

As a retrospective single-institution series, our study has certain limitations. Radiological exams were not rereviewed for the purpose of this study and the results reflect a real-world practice. We only included patients with a Bosniak III renal cyst who were surgically treated, as surgical pathology is a strong reference for the analysis. However, this is a selection bias. The size of our population was relatively limited, although only few series in the literature included >50 patients with Bosniak III lesions [13, 17, 24]. Finally, although CEUS allows the characterization of renal cystic lesions as benign or malignant with at least the same accuracy as CT imaging [25], its diagnostic ability in the case of indeterminate lesions after cross-sectional imaging might be poorer.

Conclusion

In our monocentric cohort of Bosniak III renal masses surgically treated, we found a malignancy rate of 37%. Using CEUS in addition to cross-sectional imaging to characterize indeterminate renal cysts tends to redefine Bosniak III as lesions with a lower risk of malignancy and can lead to overclassification. As a significant proportion of these lesions are benign and when malignant and are generally of low grade/low stage, their management could evolve toward initial monitoring. These changes in management of complex renal cysts would require prospective studies to assess the benefit of such practice and the risk for delayed treatment in case of cystic RCC.

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Statement of Ethics

All subjects have given their written informed consent and the study protocol was approved by the Ethical Committee of the French Association of Urology (CERU-AFU).

Author Contributions

F.A., A.M., and M.-O.T. contributed to the conception of this study. F.A. and J.S. collected the data. C.D. and J.-M.C. reviewed all the radiological exams. V.V. performed the histological examination. F.A., J.S., A.M., and M.-O.T. have drafted the manuscript or substantively revised it.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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