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Long-term oncological outcomes of cystic renal cell carcinoma according to the Bosniak classification

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Abstract

Objectives To evaluate the prognostic role of the Bosniak classification on the long-term oncological outcomes of cystic renal cell carcinomas.

Material and method In a national multicentric retrospective study, we included patients treated surgically for localized cystic RCC from 2000 to 2010. Patients with a follow-up of less than 4 years, benign tumors, and ablative treatments were excluded. The primary outcome was disease-free survival.

Results 152 patients met the inclusion criteria: Bosniak II (6%), III (53%), IV (41%), with a median follow-up of 61 (12–179) months. Characteristics of the population and the tumors were [median, (min–max)] age 57 (25–84) years old, tumor size 43 mm (20–280), RENAL score 7 (4–12), PADUA score 8 (5–14). Treatments were 55% partial nephrectomy, 45% radical nephrectomy, 74% open surgery, and 26% laparoscopy. In pathological report, cystic RCC were mainly of low grade (1–2, 77%) and low stage (pT1, 81%). The two main histological subtypes were conventional (56%) and papillary (23%) RCC. Staging at presentation and histological characteristics were similar between Bosniak III and IV, except for high grade which was more common in Bosniak IV (12 vs 36%, $p < 0.01$). The Bosniak classification was not predictive of the recurrence, as 5- and 10-year disease-free survival were similar in Bosniak III and IV (92% vs 92% and 84% vs 83%, $p = 0.60$).

Conclusion The Bosniak classification is predictive of the risk of malignancy but not of the oncological prognosis. Regardless of the initial Bosniak categories, almost all cystic RCCs were of low stage/grade and had low long-term recurrence rate.

Keywords Renal cell carcinoma · Complex renal cyst · Bosniak

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Introduction

Five to seven percent of renal cell carcinomas (RCC) have cystic component at the time of diagnosis. Distinguishing between benign and malignant cystic tumors is one of the challenges faced by urologists when dealing with complex renal cysts. In 1986, Bosniak proposed a classification which linked the radiological aspect to the risk of malignancy [1]. Complex cysts of the kidney were classified in four categories according to 6 radiological parameters: the appearance of the cyst wall, the content of the cyst, the presence of septas and/or calcifications, the enhancement of the wall of the cyst and/or its content after contrast injection. Because of its reproducibility and its ability to discriminate benign and malignant tumors, the Bosniak classification has been widely adopted and incorporated into the guidelines of complex kidney cysts management [2–5]. Two modifications were made to the original classification: the introduction of category IIF in 1993 and the reclassification of nodular calcifications to II/IIF criteria instead of III in 2003 [6, 7]. The prevalence of malignancy initially reported by Bosniak has been recently reevaluated in a systematic review of the literature conducted by Schoots et al. The risk of malignancy for Bosniak II, IIF, III, and IV were, respectively, 9% (5–14%), 18% (12–26%), 51% (42–61%), and 86% (81–89%) [8].

For Category I and II, a radiological follow-up is not recommended as they are considered to be benign [4, 5]. For IIF cysts, a 5-year radiological observation distinguishes stable cysts, that have malignancy risk of $< 1\%$, from cysts reclassified as category III/IV which have a risk of malignancy of 85% and justify a surgical removal. For Bosniak III, surgical excision or active monitoring is recommended depending on the patient's tumor characteristics and comorbidities, considering that the risk of malignancy is 51%. Surgical excision is the standard treatment for Bosniak IV cysts as the risk of malignancy is 86% [2, 3].

Although the Bosniak classification can predict the risk of malignancy, its prognostic value on the oncological outcome of cystic RCC has never been addressed in previous series. In this study, we have evaluated the long-term oncological outcome of cystic RCC according to the Bosniak category.

Material and method

Population

A national multicenter study was held in nine academic and private hospitals. All included patients had locally signed a consent for the use of clinical and follow-up data for research purposes.

Patients included were adults (≥ 18 years) treated for cystic RCC between 2000 and 2010. Cystic renal tumor and Bosniak category was determined by initial imaging report. Considering the 9 centers involved in this retrospective study were all national experts centers, a central review of the imaging was not performed.

Patients all had a surgical excision of the cystic renal tumor by partial or radical nephrectomy, and a pathological report confirming a RCC. Patients for whom pathological report concluded to a benign tumor or metastases from non-renal cancers were excluded. Metastatic RCC at the time of the diagnosis and patients with a follow-up of less than 4 years were excluded. Furthermore, patients who underwent ablative treatment or had incomplete data were also excluded from the study.

Tumor characteristics, treatment, and follow-up

Concerning the tumor characteristics: the Bosniak category, the tumor size and location, the RENAL and PADUA morphometric scores were reported. Concerning treatment, the delay between the diagnosis and the treatment, the type of treatment (partial or total surgery), and the surgical approach (open or laparoscopic) were evaluated. The stage, histologic subtype, and the Fuhrman grade were determined from the specimen. Follow-up was defined as the duration between treatment and death or the date of the latest information (in months).

Endpoints and assessments

The primary endpoint was recurrence-free survival, which was defined as the duration between the treatment and recurrence (local, contralateral, or systemic) or between the treatment and the date of the latest information for patients who had no recurrence. Secondary endpoints were TNM stage, Fuhrman grade, histological subtype, type of surgery (partial vs radical nephrectomy), specific survival, and overall survival.

Statistical analysis

Patients were stratified according to the Bosniak classification. The results are presented in median and minimum–maximum for the quantitative data, and percentage for the qualitative data. The clinical, histological, and oncological characteristics of the Bosniak categories were compared by the Chi-2 test and the continuous variables by the Mann–Whitney test. Survival was determined according to the Kaplan Meier regression method and prognostic factors for recurrence-free survival were determined by a Cox regression. Considering the low number of deaths, the multivariate analysis only concerned recurrence-free survival.

All analyzes were done with the Graphpad PRISM® and XLSTAT® for windows software. A $p < 0.05$ was considered significant. The 95% confidence interval was reported.

Results

Between January 1, 2000 and December 31, 2010, 152 patients treated for cystic RCC were identified and met the criteria of inclusion.

Clinical and demographic characteristics

The clinical and demographic characteristics of the 152 patients are summarized in Table 1. The Bosniak II, III, and IV accounted, respectively, for 6% (9/152), 53% (81/152), and 41% (62/152) of the cohort. The majority of patients were men (70.5%) and the median age at diagnosis was 57 years (25–84). Median Body Mass Index (BMI) was 26 kg/m^2 (18–41). The median Charlson comorbidity score was 3 (0–7) and the median ASA score was 2 (1–3). Median glomerular filtration rate (GFR) was 85 mL/min (10–154). The initial clinical and demographic characteristics of the patients were similar in the 3 Bosniak groups (II, III, IV) (Table 1).

Tumor morphology

The tumor characteristics according to each Bosniak category are reported in Table 2.

The median tumor size was 43 mm (95% confidence interval (CI), 43–55, range 10–280). The median RENAL and PADUA scores were, respectively, 7 (4–12) and 8 (5–14). Tumors were localized on the right kidney in 55% of the patients, and on the anterior lip in 53% of the cases. Upper, medio-renal, and lower pole tumors were, respectively, 33%, 34%, and 33%. The morphological characteristics of the tumors were well balanced between the 3 Bosniak categories (Table 1).

Characteristics of treatments

Concerning the treatments, 55% of patients had partial nephrectomies and 45% had radical nephrectomies

Table 1 Patients demographics by Bosniak stratification

	Bosniak II ($n=9$)	Bosniak III ($n=81$)	Bosniak IV ($n=62$)	p
Patient characteristics				
Age, years (mean, SD)	57 ± 14	53 ± 14	59 ± 13	0.09
Gender (%)				
M	78%	78%	60%	
F	22%	22%	40%	
IMC, kg/m^2 (mean, SD)	28 ± 3	27 ± 5	26 ± 4	0.52
Score ASA [median, (min–max)]	2 (1–3)	2 (1–3)	2 (1–3)	0.88
Score Charlson [median, (min–max)]	1 (0–5)	2 (0–7)	2 (0–7)	0.05
Renal function				
Serum creatinine, µmol/L (mean, SD)	84 ± 22	104 ± 102	107 ± 98	0.80
GFR, mL/min (mean, SD)	83 ± 20	86 ± 28	79 ± 31	0.49
Follow-up, year (mean, SD)	61 ± 35	65 ± 33	65 ± 38	0.93
Tumor morphology				
Tumor size, cm (mean, SD)	35 ± 19	49 ± 35	59 ± 45	0.25
Side				
Right, %	33%	59%	58%	0.50
Left, %	77%	41%	42%	
Location 1				
Upper pole, %	33%	38%	38%	0.96
Medium, %	50%	32%	33%	
Lower pole, %	27%	30%	29%	
Location 2				
Anterior, %	75%	49%	57%	0.54
Posterior, %	25%	51%	43%	
RENAL score, [median, (min–max)]	7 (4–10)	7 (4–12)	8 (4–12)	0.49
PADUA score, [median, (min–max)]	8 (7–9)	8 (6–12)	9 (6–11)	0.64

Table 2 Tumor and treatment characteristics by Bosniak stratification

	Bosniak II ($n=9$)	Bosniak III ($n=81$)	Bosniak IV ($n=62$)	p
Treatment				
Radical nephrectomy	67%	48%	52%	0.68
Partial nephrectomy	33%	52%	48%	
Flank incision	83%	50%	48%	0.26
Open-sub-costal	17%	24%	28%	
Laparoscopic–robotic	0%	26%	24%	
Peri-operative period				
Hospitalization, day (mean, SD)	8 ± 3	10 ± 6	8 ± 3	0.17
Pathologic category				
Stage				
pT1	34%	81%	58%	0.85
pT2	66%	13%	35%	
pT3	0%	6%	7%	
Grade				
Grade 1–2	100%	88%	64%	< 0.01
Grade 3–4	0%	12%	36%	
R0	100%	100%	100%	
Histology				
Subtype				
Conventional	17%	58%	62%	0.08
Chromophobe	33%	2%	5%	
Papillary	50%	23%	26%	
Cystic multilocular clear cell	0%	13%	7%	
Cystic conventional	0%	4%	0%	

(Table 2). The surgical approaches were as follows: flank incision (open retroperitoneal approach) in 52%, subcostal laparotomy (open transperitoneal approach) in 22%, and transperitoneal laparoscopy in 26%. The mean time between diagnosis and treatment was 4 ± 9 months and the mean hospital stay was 7 ± 4 days. Treatment characteristics were similar in the 3 Bosniak categories especially the type of surgery (Table 2).

Histological features

The histological subtypes were 56% conventional RCC, 23% papillary RCC, 3% chromophobe RCC, and 8% multilocular cystic with clear cells RCC (Table 2). The majority of tumors were of low stage: pT1a 49%, pT1b 32%, pT2 14%, pT3a 5%, and low histological grade: low grade (1–2) 77% and high grade (3–4) 23%. There was no difference in the distribution of low (pT1–2) and high (pT3) pathological stages in the 3 Bosniak categories ($p=0.85$). High grade (3–4) was significantly more common in Bosniak IV (36% vs 13% and 0%, respectively, for Bosniak IV, III, and II, $p=0.002$) (Table 2).

Follow-up, recurrence, and metastases

The median follow-up was 61 months (95% confidence interval (CI), (59 to 70), range 12 to 179). Thirteen recurrences were reported: 8 systemic recurrences, 4 contralateral recurrences, and 1 local recurrence, with a median time of 30 months after surgery (7–59). The overall and the specific survivals were, respectively, 91% and 98% at 5 years (Figs. 1, 2).

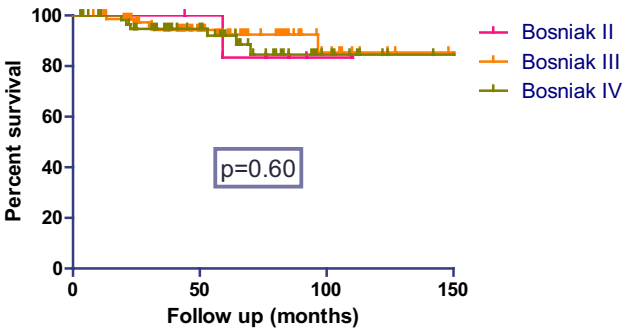

Fig. 1 Recurrence-free survival by Bosniak stratification

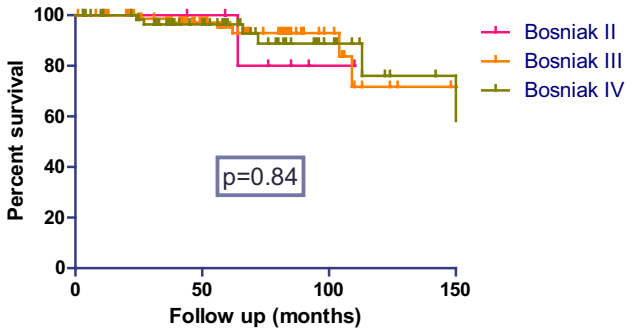

Fig. 2 Global survival by Bosniak stratification

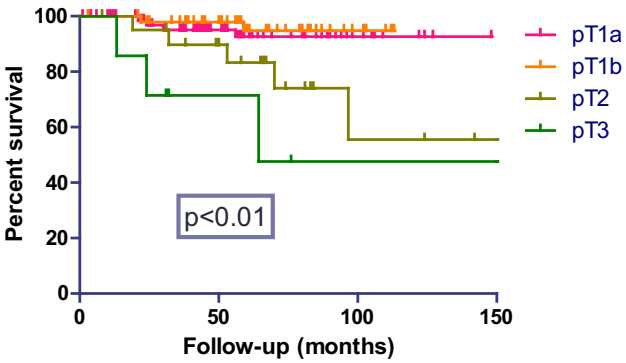

Fig. 3 Recurrence survival by stage

Survival without recurrence for Bosniak II, III, and IV tumors were, respectively, 82% versus 92% versus 92% at 5 years, and 82% versus 84% versus 83% at 10 years ($p=0.60$) (Fig. 1). The overall survival rates for Bosniak II, III, and IV were, respectively, 79% versus 95% versus 96% at 5 years, and 79% versus 71% versus 76% at 10 years ($p=0.84$). (Fig. 2).

In univariate analysis, significant prognostic factors for cancer recurrence were Fuhrman grade 4 (HZ = 28 (3–212,) $p=0.001$), stage 3a (HZ = 4 (1–16) $p=0.035$), radical nephrectomy (HZ = 3 (1–7), $p=0.029$), ASA score at the diagnosis (HZ = 3 (1–5) $p<0.01$) (Table 3) (Figs. 3, 4).

In multivariate analysis, prognostic factors for recurrence were general status (ASA score), and grade 4. Stage pT3 was not a prognostic factor of recurrence; however, the low number of events could weaken the multivariate analysis. The Bosniak classification was not statistically associated with the risk of recurrence (Table 3).

Discussion

The Bosniak classification is mentioned in all recommendations as the preferred classification for the characterization and management of complex renal cysts. This classification is predictive of the risk of malignancy which is arranged

Table 3 Prognostic factors of recurrence

	Univariate analysis				Multivariate analysis			
	Haz. ratio	*p*	(95% conf. interval)		Haz. ratio	*p*	(95% conf. interval)	
Bosniak								
Bosniak II	1				1			
Bosniak III	0.93	0.94	0.11	7.31	3.89	0.27	0.34	0.44
Bosniak IV	1.17	0.88	0.14	9.18	2.38	0.45	0.25	22.67
Grade								
1–3	1				1			
4	28.00	0.001	3.61	212.78	16.15	0.03	1.40	186.71
Stage								
1–2	1				1			
3a	4.19	0.03	1.11	15.84	0.83	0.91	0.03	23.13
Tumor size								
Continuous	1.00	0.01	1.00	1.01	1.00	0.80	0.99	1.01
Treatment								
Partial nephrectomy	1				1			
Radical nephrectomy	2.88	0.03	1.11	7.46	2.26	0.27	0.53	9.74
ASA	2.56	< 0.01	1.42	4.60	4.42	< 0.01	1.52	12.83
BMI	0.098	0.73	0.87	1.09				
Charlson	1.24	0.07	0.98	1.58				
GFR	0.98	0.04	0.96	0.99	0.98	0.07	0.94	1.00

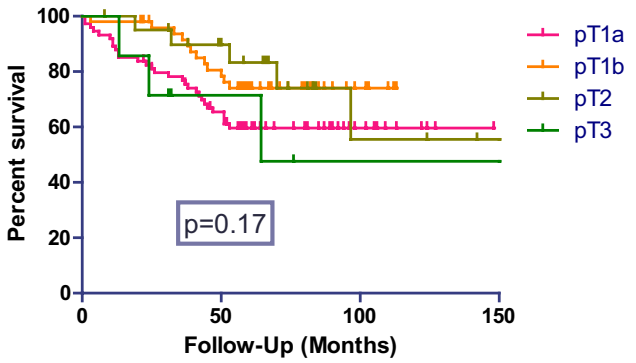

Fig. 4 Global survival by stage stratification

from less than 1% for Bosniak I to over 90% for Bosniak IV [2, 3, 8].

Cystic RCCs are known to be predominantly low-stage and low-grade tumors. In series published to date, 57–100% of cystic RCC are of low grade and a majority is of low stage (Table 4) [9–16]. These results are consistent with our series, in which the prevalence of low stage (pT1) and low (1–2) grade were, respectively, 81% and 77%. In a study comparing 678 cystic to 46,677 solid RCCs from the SEER database, Winters et al. reported that cystic RCCs were of a lower stage (T1a 66% vs 55% $p<0.001$), were better differentiated (33% vs 16%, $p<0.001$), and were smaller than solid RCC at the time of presentation (mean size 3.8 cm vs 4.5 cm, $p=0.002$) [16].

Regarding the histology of cystic RCC in our study, we found an increased prevalence of the papillary subtype of 23% versus 56% for conventional subtype, whereas the distribution of pathological stages was similar in the 3 Bosniak categories (II, III, and IV). In 2018, in a series of 175 cystic RCC, Nouhaud et al. also demonstrated that Bosniak III and IV had different histological profiles with, respectively, 46.7 versus 63.7% of conventional RCC, 30 versus 21% of papillary RCC, and 18.3 versus 0.9% of cystic multilocular RCC ($p<0.001$) [17].

Cystic RCCs consist of various pathological entities, some of which are well identified (for example, multilocular cystic RCCs), while others are cystic subtypes of common RCC. Thus 15% of clear cell RCC can have a dominant cystic presentation or occur in a cyst [18]. The papillary subtype may also occur in the form of a large cyst with hemorrhagic or necrotic content surrounded by a pseudocapsule. Less-frequent RCCs, such as cystic nephroma, stromal tumor, tubulocystic carcinoma, and RCC associated with an acquired cystic kidney disease, may also occur in the form of cysts [18–20].

In our study, despite the higher prevalence of high-grade RCC in Bosniak IV compared to Bosniak III, we found similar and favorable cancer-free survival in the Bosniak categories III and IV: 92% versus 92% at 5 years, and 85% versus 85% at 10 years ($p=0.35$). The series published in literature to date also reported favorable oncological outcomes with disease-free survivals ranging between 83% and 98% at 5 years (Table 4) [9–12, 14–17]. In 2015, Winters et al. also demonstrated that cystic RCC was associated with an improvement in cancer-specific survival when compared with solid RCC at the same stage [16]. T1a cystic and solid tumors had similar prognosis, whereas the prognosis of T1b/T2 tumors was more favorable in cystic RCC compared to similar solid RCC. The limitation of the study of Winters et al. was that Fuhrman grade and Bosniak stage were not reported, and this series also included only clear cell RCC [16].

The favorable prognosis of cystic cancers of the kidney implies specificities for the management including the possibility of offering surveillance for elderly patients and/or for patients with high comorbidities [8, 21]. In 2017, Chandrasekar et al. reported that 80.7% of 336 complex renal cysts (55.1% Bosniak IIF, 36.3% Bosniak III, and 8.6% Bosniak IV) were treated with an active surveillance. After a mean follow-up of 67.1 months, the authors reported a favorable specific survival of 99.7% (meaning only 1 specific death occured). Excluding VHL patients, the cancer-specific death rate was zero [22].

Table 4 Representative reference cohort of cystic renal cell carcinoma

	Bielsa et al.	Koga et al.	Onishi et al.	Nassir et al.	Han et al.	Webster et al.	Donin et al.	Winters et al.
Year published	1998	2000	2001	2002	2004	2007	2015	2016
Nb patients	25	21	27	12	18	85	61	678
Age, mean, years		60, 4	52	59	58		64	58
Male (%)	96		96	36	61	54	64	55
Low grade (1–2)	92%	100%	96%	100%	100%	88, 90%	93, 70%	57%
Histology RCC		90, 40%		0%			44,3	
Follow-up (mean, years)		65	82, 8	42, 5	32, 1	60	48, 4	52
5-year disease-free survival	83%	100%	84, 40%		82%	100%	100%	98%

The growth of cystic RCC is variable and does not predict either the histological subtype or tumor aggressiveness. In 2013, Jhaveri et al., published a series of 26 histologically confirmed cystic RCC who underwent a 6-month initial monitoring before the surgical excision [23]. During this observational time, the tumor diameter increased of 10.5 mm (mean) (0–24 mm) corresponding to an average growth of 46%. But diameter increase was not statistically correlated with the histological subtype or grade [23].

In our study, despite a mean tumor size greater than 4 cm at the time of surgery, the most performed treatment was partial nephrectomy (55%). Because of the potential risk of peroperative cyst rupture, radical nephrectomy could be preferred to partial nephrectomy but there is some evidence suggesting the safety of conservative treatment and laparoscopy. In 2005, Spaliviero et al. reported the outcomes of 50 laparoscopic partial nephrectomies for cystic masses. The authors assessed no peroperative cyst rupture or spillage. One retroperitoneal recurrence occurred at 1 year despite negative (R0) surgical margins. Partial nephrectomies for cystic masses were matched with 50 similar procedure for pT1a solid masses and showed similar oncological outcomes [24]. Recently, Pradere et al. reported 50 intraoperative cyst rupture in a cohort of 268 radical/partial, open/laparoscopic nephrectomies. Although 75% of cyst that ruptured were malignant, neither peritoneal carcinomatosis nor port site metastases were reported. Estimated recurrence-free rate was similar between patients with versus without intraoperative cyst rupture (100% vs 92.7% at 5 years, $p = 0.20$) [25].

The main limitations of our study were its retrospective nature and the lack of a systematic centralized reviewing of preoperative imaging, which could lead to a bias in the initial Bosniak category allocation. There was an imbalance in the Bosniak II cohort, that reflects current practice in the management of Bosniak II: the systematic review by Schoots et al. concluded that only 12% of Bosniak IIF cyst will progress during follow-up and need a surgical excision because of a high risk of malignancy [8]. The limited number of patients was a consequence of the strict exclusion/inclusion criteria that were required to explore specifically the prognostic value of the Bosniak classification in long-term oncological outcomes. All benign tumors were excluded, while they account for 50% of Bosniak III and more than 80% of Bosniak II according to the systematic review by Schoots et al [8]. Prospective multicentric studies are needed to improve the level of evidence of our conclusions.

Conclusion

In this survey, cystic renal cell carcinomas (cRCC) were predominantly of low grade and low stage. The distribution of histological subtypes and pathological stages was similar between Bosniak categories III and IV although a high histological grade was more common for Bosniak IV. We concluded that the Bosniak classification was not predictive of long-term recurrence and oncologic outcome, as disease-free survivals of Bosniak III and IV was, respectively, 92% and 92% at 5 years, 84% and 83% at 10 years.

Author contributions RB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Protocol/project development: Boissier, Bensalah. Data collection or management: Chkir. Chelly, Dariane, Khene, Giwerc, Allenet, Lefrancq, Gimel, Hetet. Data analysis: Boissier, Bensalah. Manuscript writing/editing: Boissier. Other (please specify briefly using 1 to 5 words): Critical revision of the manuscript for important intellectual content: Nouhaud, Bigot, Bernhard, Long, Gimel, Bodin, Ouzaid, Rioux-Leclercq, Correas, Albigès, Mejean.

Compliance with ethical standards

Conflict of interest Authors reported no conflict of interest regarding this study.

Research involving human participants and/or animals All included patients had locally signed a consent for the use of clinical and follow-up data for research purposes. The study was approved by the ethics committee of Association Francaise d'Urologie.

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