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ORIGINAL ARTICLE

Management, pathology and outcomes of Bosniak category IIF and III cystic renal lesions

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Abstract
Objective To analyze the management, pathology and outcomes of Bosniak category IIF and III cystic renal lesions.
Methods This retrospective study included 85 consecutive patients with Bosniak category IIF and III lesions, who were actively surveilled or surgically treated at three academic urology centers between 2003 and 2012. Outcomes of interest included the rates of cyst progression and pathology.
Results Overall, 27 patients with Bosniak category IIF lesions were initially managed by active surveillance, from which eighteen (67 %) did not progress after a median interval of 64 months, while 9 (33 %) underwent surgery within a median interval of 18 months. There were 58 patients with Bosniak category III lesions, 54 (93 %) of which were managed by surgery. Compared with Bosniak category IIF, Bosniak category III lesions had more frequently proven RCC (64 vs. 30 %, $p = 0.005$). Of the tumors that underwent surgical extirpation, the T stage, grade ($p = 0.65$) and subtype distribution ($p = 0.36$) did not differ between the Bosniak categories. The majority of RCCs were low-stage and low-grade tumors. One patient developed a local recurrence. There were no RCC-specific deaths.
Conclusions As only a minority of Bosniak IIF lesions are malignant and the majority are low-stage and low-grade tumors, initial active surveillance is the standard of care for these lesions. Progressive Bosniak IIF lesions may undergo later RCC treatment without seemingly loosing the window of cure. Bosniak III lesions harbor a high risk of malignancy and should be managed as solid renal tumors according to contemporary guidelines.

Keywords Cyst · Bosniak · Progression · Kidney cancer · Surveillance · Surgery

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Introduction

The Bosniak classification is considered the standard radiological evaluation scheme of cystic renal lesions. It was initially developed on CT findings [1], but is similarly applicable to magnetic resonance imaging (MRI) [2]. The overall incidence of renal cell carcinoma (RCC) in each Bosniak category did not change over the past 20 years [3]. Contemporary studies show that RCC is found in 25 and 50 % of Bosniak category IIF and III lesions, respectively [4].

The overall incidence of malignancy in the Bosniak categories IIF is influenced by three factors: (1) surgery after diagnosis without an initial observation period, what eliminates the possibility to prove the stable and presumably benign character overtime, (2) patient's and physician's desire for surgery and (3) inter-observer variability in the Bosniak classification [5]. At many centers, Bosniak

category IIF lesions are initially managed by active surveillance. Surgery may be offered to younger patients or those who fear RCC or progression. There is, however, no consensus regarding the length of surveillance. Many consider Bosniak category III lesions a "surgical lesion," as the rate of malignancy is about 50 %. However, the RCCs are frequently low-stage and low-grade tumors [6, 7], which make this approach questionable. In all, there are only few reports with relatively short follow-up periods [4, 5, 8–11].

As both categories pose some dilemmas for radiologists and urologists and their patients, we evaluated data from three academic urology centers. The aim of our study was to analyze the management, pathology and outcomes of Bosniak IIF and III cysts in a contemporary cohort.

Patients and methods

Study design

The aim of this retrospective study was to analyze the management, pathology and outcomes of Bosniak category IIF and III cystic renal lesions. We identified 128 patients who were actively surveilled or surgically treated at three tertiary academic urology centers between 2003 and 2012. Prior to study initiation, all participating centers approved the data-sharing agreement and obtained approval by their institutional review board. Thirty-nine patients were excluded due to a surveillance interval of less than 18 months, polycystic kidney disease or a history of RCC, leaving 85 patients as final study cohort.

Management approach

Clinical decision-making processes were similar among the three centers. All patients underwent an ultrasound plus a 4-phase contrast-enhanced CT scan or an MRI of the abdomen. The lesions were classified according to the Bosniak scheme by one radiologist at each institution.

Partial or radical nephrectomy was recommended for all cases with Bosniak category III lesions, which was consistent with guidelines RCC treatment [12]. Patients with Bosniak category IIF lesions entered a surveillance protocol with biannual CT/MRI scans for a total of 2 years and annually thereafter. All imaging studies were performed with and without intravenous iodine/gadolinium contrast medium. Slice thickness was 2.5–5 mm. Surgery was recommended in case of progression, which was defined as an increase in Bosniak category, presence of new solid nodules or enhancement, increase in numbers of septa, thickening of septa and an increase in size of more than 20 % from the initially largest axial diameter. Increase in size alone was not a trigger for intervention, only in conjunction with changes in internal architecture and progression of enhancement.

Analyzed variables

Data were prospectively collected in a computerized database and included age, gender, radiological tumor size, Bosniak category, histology and follow-up. Multilocular cystic RCC, cystic RCC as well as RCC with cystic degeneration were included in the clear cell group.

Statistical analysis

Variables are presented as numbers and proportions or as median and interquartile range (IQR). Significance testing was performed with Fisher's exact tests and Kruskal–Wallis tests, as appropriate. All statistical testing was performed with R 3.0.1, and a p value <0.05 was considered statistically significant.

Results

Patient characteristics

Bosniak categories IIF and III were assigned to 27 (32 %) and 58 lesions (68 %), respectively. Characteristics are summarized in Table 1.

Management and pathology

The 27 patients with Bosniak category IIF lesions were initially managed by active surveillance, 18 of which did not progress after a median (IQR) interval of 64 months (34–75 months). Of the 9 patients (33 %), who underwent delayed surgery after a median interval of 18 months, 8 (89 %) were found to have RCC. Changes in internal architecture and progression of enhancement were the main indications for intervention: three lesions exhibited new cyst-wall enhancement (>20 HU), three showed a change in internal architecture (increased number of septa with additional irregular thickening), one demonstrated pathological enhancement in the septum and two exhibited a significant growth in size >20 % in conjunction with new borderline enhancement (15–20 HU). The latter lesions were >6 cm, and the enhancement, but not the increase in size, was the trigger for intervention. Taken together, RCC was proven in 30 % of Bosniak category IIF lesions (Table 1).

There were 58 patients with Bosniak category III lesions, 54 (93 %) of which were managed by surgery. Four patients refused surgery and were actively surveilled for a median of 43 months. One of these lesions progressed to

Table 1 Clinical and pathological characteristics of 85 patients presenting with Bosniak category IIF and III cystic renal lesions

Variable	Total	Bosniak IIF	Bosniak III	*p* value
n	85	27	58	–
Age–median (IQR)	60 (51–69)	61 (48–69)	59 (51–69)	0.95
Male–*n* (%)	49 (58)	14 (52)	35 (60)	0.49
Size–median (cm, IQR)	3.7 (2.5–5.5)	3.4 (2.4–4.9)	3.7 (2.5–5.5)	0.65
Surgery–*n* (%)	63 (74)	9 (33)	54 (93)	<0.001
Partial nephrectomy–*n* (%)	45 (53)	8 (89)	37 (69)	0.43
Proven RCC–*n* (%)				
Total cases	45 (53)	8 (30)	37 (64)	0.005
Surgical cases	45 (71)	8 (89)	37 (69)	0.43
Subtype				
Benign	18 (29)	1 (11)	17 (31)	0.36
Clear cell	31 (49)	5 (56)	26 (48)	
Papillary	14 (22)	3 (33)	11 (20)	
TNM stage–*n* (%)				
pT1a N0 M0	30 (67)	5 (63)	25 (68)	0.65
pT1b N0 M0	7 (16)	2 (25)	5 (14)	
pT2a N0 M0	4 (9)	1 (13)	3 (8)	
pT3a N0 M0	4 (9)	0	4 (11)	
Fuhrman grade–*n* (%)				
G1	29 (64)	6 (75)	23 (62)	0.75
G2	15 (33)	2 (25)	13 (35)	
G3	1 (2)	0	1 (3)	

Compared with Bosniak IIF, Bosniak III cysts were more frequently RCC, while the stage, grade and subtype distribution did not differ

Bosniak category IV, but the patient refused an intervention. Among the 54 patients, who underwent surgery, 37 (69 %) were diagnosed with RCC. Malignancy was proven in 37 of the 58 Bosniak III lesions (64 %). There was no association of size and the incidence of RCC (mean size: 5.0 vs. 4.3 cm, $p = 0.42$).

Of the tumors that underwent surgical extirpation, the stage ($p = 0.65$), grade ($p = 0.75$) and subtype distribution ($p = 0.36$) did not differ between the Bosniak categories (Table 1). All T3 and grade 3 lesions were classified as Bosniak III (Table 2).

All specimens showed negative margins on final histology. Frozen section analysis regarding the dignity of the cyst and the surgical margin was done at the surgeon's discretion, but this did not change the surgical approach in a single case.

Outcomes

The median (IQR) follow-up after surgery for RCC was 36 months (28–57 months). One patient with a 1.5 cm Bosniak III cyst that turned out to be clear cell RCC (pT1aN0M0G1) developed recurrence in the same kidney and was managed with a second partial nephrectomy. There were no deaths from RCC. No patient developed metastatic disease and none developed a *de novo* complex cystic renal lesion.

Discussion

We analyzed the management, pathology and outcomes of patients with Bosniak category IIF and III cystic lesions.

Table 2 Clinical and pathological characteristics of pT3 and grade 3 lesions

Age	Gender	Size (cm)	Bosniak category	Surgery	Subtype	TNM	Grade	FU (months)
71	Male	2	3	PN	Clear cell	T3aN0M0	2	35, NED
52	Female	5	3	RN	Clear cell	T3aN0M0	2	29, NED
63	Male	5	3	PN	Clear cell	T3aN0M0	2	35, NED
47	Male	3.5	3	PN	Papillary type 1	T3aN0M0	2	33, NED
42	Male	1	3	PN	Papillary type 2	T1aN0M0	3	26, DOOC

PN partial nephrectomy, *RN* radical nephrectomy, *NED* no evidence of disease, *DOOC* died of other causes

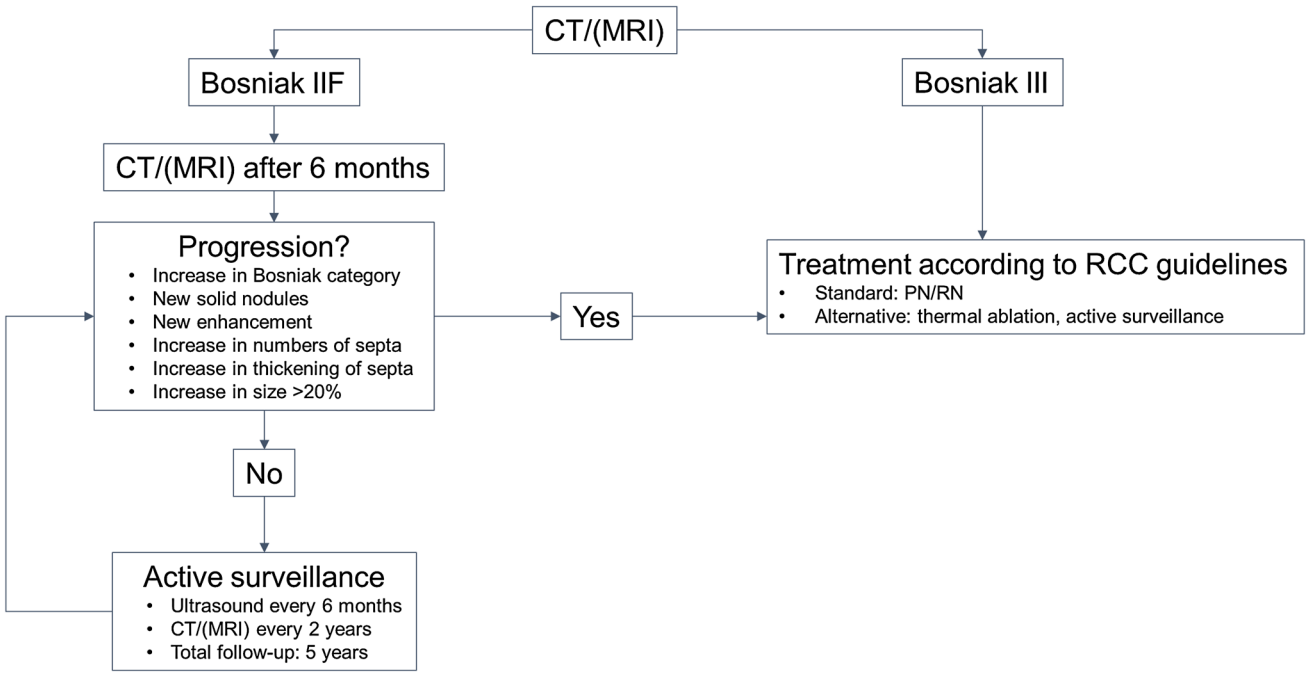

Fig. 1 Institutional protocol for management of Bosniak category IIF and III cystic renal lesions. The protocol was developed according to the evidence from the literature. The flowchart underlines the importance of strict follow-up in Bosniak IIF lesions, which should be done by experienced urologists and radiologist

We confirm that only about 30 % of Bosniak IIF lesions are malignant; therefore, active surveillance for up to 5 years should be the initial standard of care. Progressive Bosniak IIF lesions may be removed surgically. This approach led to a large proportion of malignant lesions, the majority of which remained low-stage and low-grade RCCs despite the delayed intervention supporting the safety of this approach. Bosniak III lesions harbor a high risk of malignancy and may be managed like solid renal tumors according to contemporary guidelines [12, 13].

Among the Bosniak IIF group, less complex and more complex lesions are distinguished. For the former group, a follow-up of 1–2 years may be sufficient, while the latter group may require repeated imaging for at least 4 years [14]. Bosniak IIF lesions that do not change within 2 years may be followed with another CT/MRI 24 months later [5]. This approach avoids unnecessary radiation. Even if about one-third of patients harbor a low-stage RCC, the risk of loosing the window of cure appears minimal if intervention is done at the appropriate time. The proportion of Bosniak IIF lesions that progress under active surveillance and may require surgery lies between 7 and 20 %. Such an approach leads to malignancy rates of 25–100 %, depending on patient cohort and criteria for active treatment [4, 5, 8, 9, 11]. All series were very small, and limited conclusions can be drawn. In addition, there is still no general agreement on the definition of cyst progression requiring surgery.

In agreement with the literature, we found that cystic RCCs (multilocular cystic RCC, cystic RCC and RCC with cystic degeneration) are usually low-stage and low-grade tumors, with an excellent prognosis [4, 5, 8, 11]. Therefore, it may be possible to offer patients with progressive Bosniak IIF lesions active surveillance or ablation as an alternative to surgery.

Imaging protocols regarding Bosniak IIF lesions vary and largely depend from the urologist's and the radiologist's experience. There are no guidelines with respect to active surveillance of these lesions. Bosniak proposed the first follow-up CT 6 months after the initial examination. If the lesion does not progress, surveillance should be repeated in yearly intervals [10]. According to our data and the literature on the natural history of solid and cystic renal masses, we have now updated our institutional guideline (Fig. 1). With this approach, it is possible that discrete changes in the internal architecture are missed, but it appears that this does not translate in an oncological compromise. The CT scan is our primary imaging modality.

Parameters of cyst progression are a matter of debate. Gabr et al. [15] demonstrated that the incidence of RCC does not depend from growth overtime, but from progression of internal architecture and enhancement. Similar data were recently reported by other groups [4, 11]. Patients with coexisting Bosniak IV lesions, solid renal masses or history of RCC are at higher risk of harboring a malignancy [4]. In

terms of size, both progressive and nonprogressive Bosniak IIF cysts tend to grow, irrespective of their change in internal architecture. Although surgical intervention was recommended in lesions with persistent growth of more than 5 mm per year [15], there is no clear consensus at what level one should intervene. One should keep in mind the known inter- and intra-observer variation in size measurement. It is our policy to consider the increase in size (>20 % of the largest diameter) as progression, but to proceed to surgical intervention only if there are additional changes in internal architecture or progression of enhancement.

At least 50 % of Bosniak III cystic lesions are RCCs [6, 15–17]. Similarly to Bosniak IIF lesions, the majority are low-stage and low-grade tumors. Even with sophisticated new imaging technologies, it is not possible to accurately identify the malignant lesions that may need an intervention. For a long time, percutaneous biopsy was not recommended because of high rates of false-negative results, but recent studies indicate a high diagnostic yield of this procedure [18]. In addition to a large spectrum of malignant lesions [19], the spectrum of benign Bosniak III lesions comprises simple cysts, hemorrhagic cysts, abscesses, multilocular cystic nephroma and mixed epithelial stromal tumor [17], and it is currently not possible to stratify this spectrum of benign lesions accurately by imaging alone. The role of other new imaging modalities remains unclear [20, 21].

At intermediate-term follow-up, the rate of metastatic progression is 0 % [1, 7, 16], but studies with long-term follow-up are lacking. There are no data to support the dogma that surgical resection of Bosniak III lesions improves cancer-specific survival. The general view on the management of Bosniak III lesions may therefore be changing, and the former "Bosniak III equals surgery" approach may no longer be valid. Lesions may be treated according to contemporary guidelines on renal tumors. This may include surgery, ablation or active surveillance [12, 13]. It was believed for a long time that ablation is not efficient in cystic lesions, but recent data show excellent oncological and functional outcomes [16]. However, thermal ablation for cystic lesions should be considered experimental, as there are no sufficient data to support it as standard procedure. It may, however, be an option for patients with significant comorbidity, who have an increased risk of perioperative complications [22].

In our study, the general patients' compliance with conservatively treated lesions was fairly high, as all included patients were followed at our academic institutions. This ensured a consistent follow-up regimen and imaging analysis by expert radiologists, while the number of included patients was low. The overall true picture of follow-up compliance among patients with Bosniak IIF and III cysts remains unknown. There are many other issues related to compliance, including the patient's anxiety about following these lesions.

This study has additional limitations. We analyzed a relatively small cohort of patients, and the study is retrospective in nature, introducing selection bias. We were not able to include about 30 % of patients because of insufficient, incomplete or short-term follow-up data. This underlines the need for strict and centralized surveillance. We have previously demonstrated a considerable rate of inter-observer variation in Bosniak II and IIF lesions [5], and we did not account for this. However, one expert radiologist at each center interpreted the imaging studies. While centralized imaging review would be desirable, it was not performed for this retrospective study. The possible differences across the institutions are reflective of the "real world" and may make the conclusions more generally applicable. Finally, the true RCC incidence in Bosniak IIF lesions remains unknown, because most are not surgically explored. It can be calculated in two different ways, either from surgically explored lesions only or by including the overall number of stable lesions that are presumed to be benign. Both ways are not entirely appropriate, as a radiographically stable lesion does not equal a benign lesion. Lumping both nonsurgically and surgically explored lesions is based on the observations by Israel and Bosniak [10]. Until proven otherwise, stable Bosniak IIF lesions may still be considered as benign.

Conclusions

As only a minority of Bosniak IIF lesions are malignant and the majorities are low-stage and low-grade tumors, active surveillance is the standard of care. Progressive Bosniak IIF lesions undergo delayed treatment, and this does not translate in an oncological compromise. Bosniak III lesions harbor a high risk of malignancy and may be managed as solid renal tumors.

Conflict of interest The authors declare no conflict of interest.

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