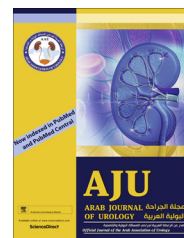




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ONCOLOGY/RECONSTRUCTION

ORIGINAL ARTICLE

A practical guide and decision-making protocol for the management of complex renal cystic masses



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Complex renal;
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ABBREVIATIONS

BCS, Bosniak classification system;
(CE)US, (contrast-enhanced) ultrasonography;

Abstract Objectives: To analyse the management, pathology and outcomes of complex renal cystic masses (CRCM) and to develop a decision-making tool for daily clinical care using the Bosniak classification system for CRCM.

Patients and methods: A comprehensive dataset of 185 patients with 188 CRCM and a minimum follow-up of 3 years were analysed for management, pathology and outcomes.

Results: We analysed 35 Bosniak II, 34 Bosniak IIF, 58 Bosniak III, and 61 Bosniak IV lesions. The overall incidence of renal cell carcinoma was 8.6%, 29.4%, 62.1%, and 78.7% for each category. Based on our surveillance strategy of Bosniak IIF masses, we recommend computed tomography (CT)/magnetic resonance imaging (MRI) every 2 years after the initial examination. We also recommend performing one MRI (as an adjunct to CT) during the early follow-up period (< 4 years). The use of MRI correlation for differential diagnostic purposes has proven useful for marginal Bosniak II, IIF and III cases.

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CRCM, complex renal cystic masses; EAU, European Association of Urology

Conclusions: From our data, we have created a decision-making protocol to guide urologists in planning a safe and effective diagnostic and treatment strategy for CRCM. The Bosniak classification is a useful tool for clinical decision-making. Uncertainties still remain for Bosniak IIF and III lesions. Our protocol shows that individualised decision-making is necessary in a significant proportion of CRCM.

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Introduction

The Bosniak classification system (BCS) for cystic renal lesions was developed based on CT findings [1]. The BCS is reader dependent and prone to inter- and intra-reader variations [2–4]. Israel et al. [5] showed that the BCS in CT and MRI are similar in most cystic renal lesions. With regard to recent evidence, MRI and contrast-enhanced ultrasonography (CEUS) tend to downgrade/upgrade some lesions and are therefore recommended as additional diagnostic tools for borderline cases [6–8]. Data suggest an individualised approach to reduce unnecessary surgical interventions, especially for Bosniak IIF and III lesions [6,9–11]. However, to date, no other systematic approach has been more accurate at predicting the malignant potential on final histology [1].

Decision-making for further diagnostics and management of cystic renal lesions is a frequent clinical task. However, there are no straightforward guidelines for appropriate management that can be applied in the daily setting, with most recommendations being based on expert opinion. In the present study, we aimed to establish a practical guide for primary care and office urologists based on our multi-institutional dataset. In addition, we propose a surveillance scheme for complex renal cystic masses (CRCM) and histologically confirmed RCC.

Patients and methods

The aim of this retrospective study was to analyse the management, pathology and outcomes of CRCM and to develop a decision-making tool for daily clinical care. However, Bosniak IIF lesions were prospectively followed, and retrospectively evaluated. We studied 190 patients who were diagnosed with a total of 199 CRCM at three tertiary academic urology centres (University hospitals of Bratislava, Slovakia; Pilsen, Czech Republic; Vienna, Austria) between 2004 and 2013. All participating centres received ethical approval by their Institutional Review Board. Only patients with ≥ 3 years follow-up were included for the final analysis. Patients with known polycystic kidney disease, Von Hippel–Lindau disease, family history of RCC, and previous surgery for RCC, were excluded from the study, leaving 185 patients with 188 lesions in the final cohort.

Management approach

The clinical decision-making processes were similar amongst the three centres. As we were continuously collaborating on our data [2,12], the general management did not differ. All patients underwent conventional ultrasonography (US) and four-phase contrast-enhanced CT or MRI of the abdomen. All imaging studies were performed with and without i.v. iodine/gadolinium contrast medium. Slice thickness varied between 2.5 and 5 mm. All lesions were classified according to the BCS by a senior radiologist at each institution.

The final indication for surgery was made by experienced urologists. Partial or radical nephrectomy was recommended for cases with Bosniak category III and IV lesions, which was consistent with guidelines on RCC treatment at that time [13]. All the surgeons tended to favour partial nephrectomy, when technically feasible. Patients with Bosniak category IIF lesions entered a surveillance protocol with biannual CT/MRI for a total of 2 years and annually thereafter. Surgery was recommended in cases 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 or an increase in size of $> 20\%$ from the initially single largest axial dimension [12].

Analysed variables

Data were retrospectively collected in a computerised database and included: age, gender, symptoms, radiological tumour size, Bosniak category, histology, and follow-up. Histology was coded as malignant or benign. In case of RCC, the 2010 TNM stage, the histological subtype, and the Fuhrman grade were recorded. The histological slides were evaluated by a senior genitourinary pathologist at each institution. Multilocular cystic clear cell RCC, cystic RCC, as well as RCC with cystic degeneration, were included in the clear cell group.

Statistical analysis

The primary point of interest was to analyse the management, pathology, and outcomes at the three academic centres. The secondary point of interest was to develop a decision-making protocol for daily clinical

care. Variables are presented as numbers and proportions or as medians. Significance testing was performed with Fisher's exact and Kruskal–Wallis tests, as appropriate. All statistical testing was performed using R 3.0.1 (The R Foundation for Statistical Computing, Vienna, Austria), and a $P < 0.05$ was considered statistically significant. All P values are two-sided.

Results

We analysed 35 Bosniak II, 34 Bosniak IIF, 58 Bosniak III and 61 Bosniak IV lesions. The overall incidence of RCC was 8.6%; 29.4%; 66.7%; 82.8% for each category, respectively, for all surgically treated masses (Table 1). Most lesions were detected incidentally. The incidence of symptomatic lesions was two (5.7%); one (2.9%); 10 (17.2%); and six (9.8%) in the Bosniak categories, respectively.

Bosniak II ($n = 35$)

After a median follow-up of 55 months, there was only one progression in size; however, size increase alone was not an indicator for surgery. In 10 patients MRI was indicated, because the lesions were more complex

on US than on CT. Two lesions were upgraded to Bosniak IIF, but remained stable and did not require intervention. Seven patients underwent laparoscopic surgery because of flank pain or a size of > 7 cm. RCC was confirmed in three of these seven patients, all three lesions were asymptomatic. The suggestion of surgery was made by a urologist considering the lesion size and technical possibility of performing a nephron-sparing surgery in relatively young and healthy patients.

Bosniak IIF ($n = 34$)

The median follow-up was 48 months. Six of 34 lesions progressed, including two in size, two with increased number of calcifications, and two developed typical enhancement. All lesions were initially diagnosed by CT. In all, 22 patients (64.7%) had MRI as well. In two cases, MRI showed more septae/enhancement and the lesions were upgraded into Bosniak III category. Both patients refused surgery, but did not progress under active surveillance. In one patient, a marginal enhancement in the cystic wall was present; however, the lesion was not upgraded (final histology confirmed RCC). In another two cases, the lesion was classified as indeterminate on CT, and according to MRI finally

Table 1 The patient's characteristics and outcomes.

| Variable | BCS category | | | | P |
|--|--------------|-------------|-------------|------------|-----------|
| | II | IIF | III | IV | |
| N | 35 | 34 | 58 | 61 | – |
| Mean (SD) | | | | | |
| Age, years | 62.8 (12.3) | 59.8 (11.8) | 59.1 (13.4) | 60.5 (9.1) | 0.51 |
| Size, cm | 3.8 (2.3) | 4.0 (2.4) | 4.4 (2.7) | 5.0 (3.1) | 0.16 |
| N (%) or n/N | | | | | |
| Female | 15 (42.9) | 15 (44.1) | 23 (39.7) | 23 (37.7) | 0.92 |
| Right sided | 18 (51.4) | 18 (52.9) | 26 (44.8) | 32 (52.5) | 0.82 |
| Symptoms | 2 (5.7) | 1 (2.9) | 10 (17.2) | 6 (9.8) | 0.12 |
| Surgical intervention | 7 (20.0) | 11 (32.4) | 54 (93.1) | 58 (95.1) | < 0.001 |
| Surgical procedure | | | | | < 0.001 |
| Nephron-sparing surgery | 7/7 | 10/11 | 37 (68.5) | 22 (37.9) | |
| Nephrectomy | 0 | 1/11 | 17 (31.5) | 36 (62.1) | |
| RCC* | 3/7 | 10/11 | 36 (66.7) | 48 (82.8) | 0.028 |
| RCC ⁺ | 3 (8.6) | 10 (29.4) | 36 (62.1) | 48 (78.7) | < 0.001 |
| RCC subtype | | | | | 0.29 |
| Clear cell | 1/3 | 6/10 | 23 (63.9) | 34 (70.8) | |
| Papillary | 1/3 | 4/10 | 12 (33.3) | 9 (18.8) | |
| Chromophobe | 0 | 0 | 0 | 2 (4.2) | |
| Other (tubulocystic, sarcomatoid features) | 1/3 | 0 | 1 (2.8) | 3 (6.2) | |
| TNM | | | | | 0.70 |
| T1N0M0 | 2/3 | 9/10 | 30 (83.3) | 36 (75.0) | |
| T2N0M0 | 1/3 | 1/10 | 3 (8.3) | 6 (12.5) | |
| T3N0M0 | 0 | 0 | 3 (8.3) | 6 (12.5) | |
| Grade | | | | | 0.13 |
| G1 | 2/3 | 8/10 | 22 (61.1) | 21 (43.8) | |
| G2 | 1/3 | 2/10 | 13 (36.1) | 18 (37.5) | |
| G3–4 | 0 | 0 | 1 (2.8) | 9 (18.8) | |

* Surgically treated patients.

⁺ All patients with confirmed RCC (the clear cell RCC group included: cystic RCC, multilocular cystic RCC, and RCC with cystic degeneration).

designated into Bosniak IIF and III categories, respectively. In both cases, the urologist decided to perform partial nephrectomy, with a positive finding of cancer (Table 1). One of those patients with a Bosniak IIF lesion was relatively young and had a fear of having cancer. According to the MRI correlation, we were able to optimise the treatment strategy in five cases (22.7%). In the remaining cases, MRI findings correlated with the CT. Eleven patients (32.4%) underwent surgery. The overall incidence of cancer was 29.4%. Only one large symptomatic lesion was benign. However, 10 of the 11 extirpated lesions were RCCs, but all were low grade (Table 1).

Bosniak III (n = 58)

Flank pain as the only symptom was present in 10 cases (17.2%). In 21 (36.2%) cases, we performed an MRI for further diagnostics. A BCS upgrade (9.5%) was detected in two cases (one lesion later regressed partially, one remained stable). Although in 10 cases it did not lead to a change in Bosniak classification, more worrisome features in terms of septal thickness and borderline/or typical enhancement were found. Surgery was performed in all 10 cases, and all lesions were RCC. In

all, 54 patients underwent surgery and the remaining four were put under observation (Table 1). The incidence of high-grade lesions was very low, just one. There was no recurrence or metastatic spread and there were three deaths from other causes.

Bosniak IV (n = 61)

Flank pain was present in six patients (9.8%), but this did not correlate with lesion size. Overall, 58 patients (95.1%) underwent surgery. We found a wide range of benign entities in 13 patients (21.3%): small organised haematoma in the cyst wall (one), oncocytoma (two), chronically infected cyst (three), haemorrhagic cyst with organised haematoma (two), low fat angiomyolipoma (one), and cystic nephroma (one). In both oncocytomas and the angiomyolipoma, the cystic component was predominant on the final histological evaluation. In three patients, under active surveillance, the histology was not available. The incidence of high-grade lesions was 18.8% (nine patients) (Table 1). After surgery, there was one local recurrence and two cases of metastatic spread with subsequent death.

Flowcharts of the institutional practice patterns for the management of CRCM are shown in Figs. 1 and 2.

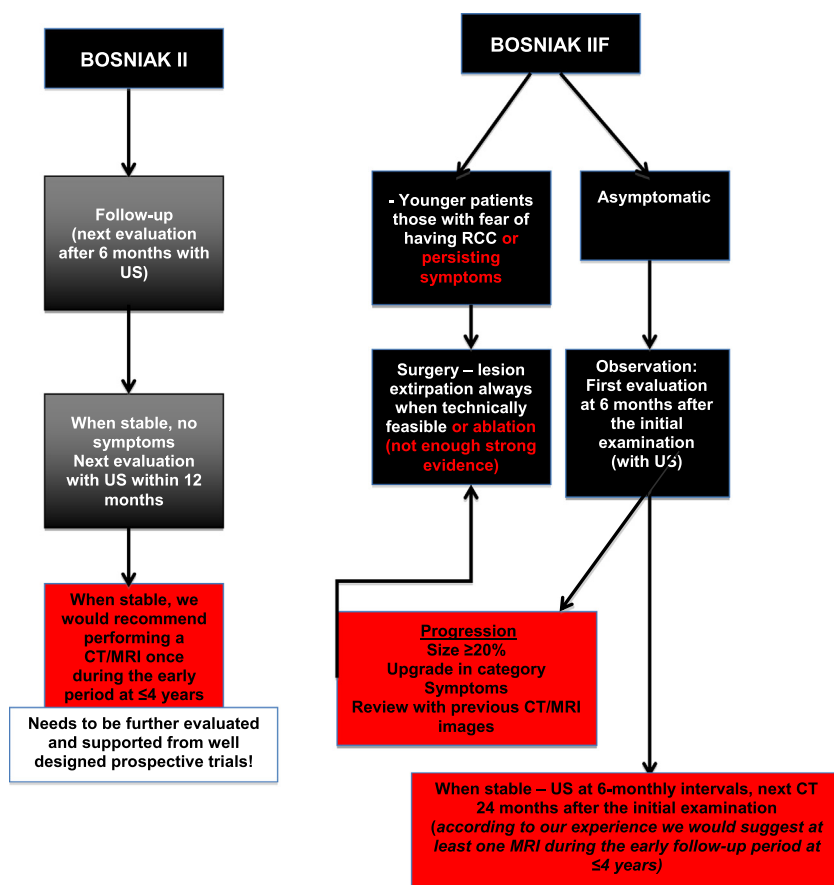


Fig. 1 Institutional practice patterns of the management of CRCM presumed to be benign according to the BCS. For symptomatic lesions surgical treatment is recommended. Partial nephrectomy with CRCM extirpation is the treatment of choice for all cases regardless of the lesion size, and whenever technically feasible.

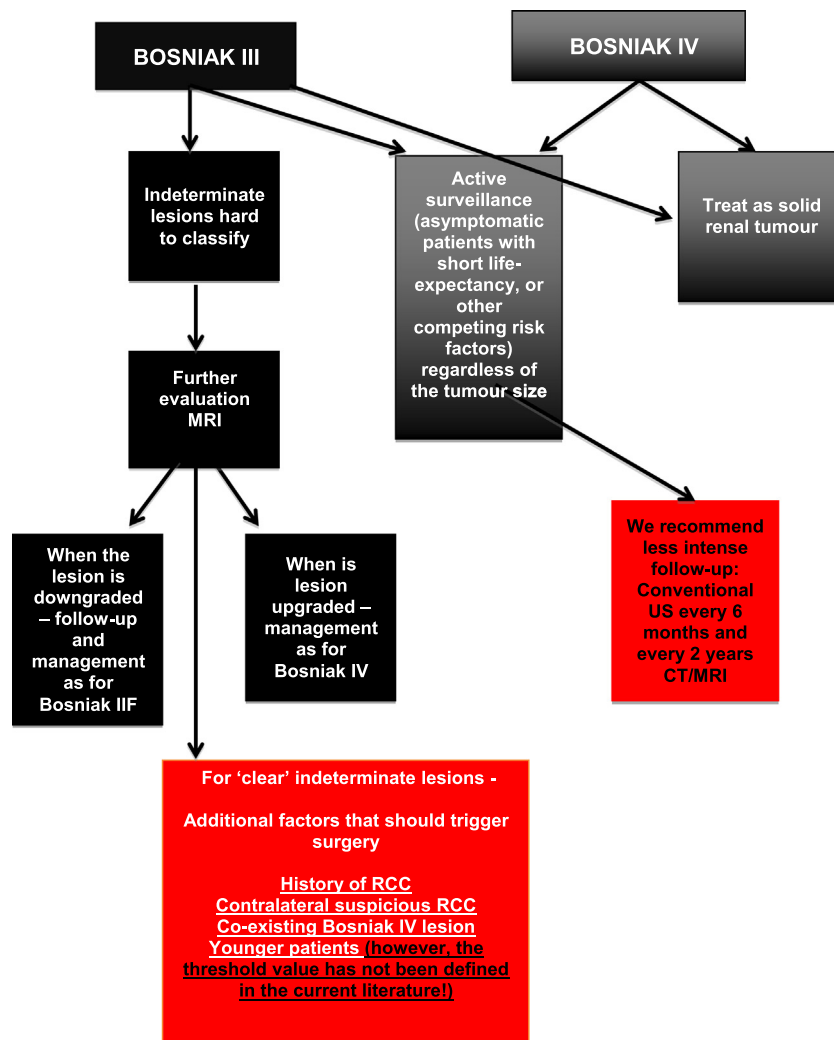


Fig. 2 Institutional practice pattern and practical guide to the management of CRCM rated as surgical lesions according to the BCS. For follow-up purposes the authors recommend CT or MRI with contrast agent. However, to avoid radiation exposure clinicians should consider MRI as the primary tool or CEUS, although calcified lesions should be evaluated with CT in the interval.

Discussion

The present study is the first to describe an updated clinical flow chart for the management of CRCM. It is probable that most urologists in tertiary centres tend to manage these patients similarly, but this guide can be used by primary care or office urologists to counsel their patients appropriately. The major known drawback of the BCS is the substantial inter- and intra-observer variation, specifically in the Bosniak IIF and III categories [2–4]. The confidence in agreement is also experience dependent: ‘The more skilled radiologist the less decrease in confidence with regard to CT or MRI’ [4,14]. Even in the era of modern imaging, we still perform 40–50% of surgeries for benign lesions in the Bosniak III category [12,15,16].

From our perspective, for indeterminate Bosniak III cases we usually recommend further diagnostics with

MRI. In some cases we can downgrade the lesion and save the patient from unnecessary intervention.

CEUS is another acceptable alternative, which can be used for surveillance purposes. We recognise that we have very limited experience in this area. Despite that fact, we think that this examination should be included in the future protocols based on emerging evidence. Recently Chen et al. [7] showed that CEUS has higher diagnostic sensitivity and accuracy but lower specificity than MRI for classifying CRCM, and was the first study to demonstrate the superiority of CEUS. However, comparative studies on new imaging modalities are limited and cannot be used as a standard reference yet [8]. Image-guided biopsy or aspiration cytology is not conclusive in a significant proportion of cases. As we know from the literature, we can easily miss the cancer and the presence of neoplastic cells in an adequate volume of aspirated fluid can be low [17]. Therefore, we have to

consider all these examinations as an adjunct to our diagnostic protocol rather than a basic examination. In addition, regardless of this we are not biopsy advocates, there is not enough convincing evidence to do otherwise. Patients with symptomatic suspicious inflammatory cystic lesions are the ideal candidates, where such an approach can be diagnostic and therapeutic as well.

True Bosniak II lesions are benign lesions that do not require follow-up [10]. According to our present results, 8.6% of the lesions were found to be RCC. For haemorrhagic cysts or partially septated with hyperdense material, we would recommend one imaging (CT/MRI/CEUS) within a period of 4–5 years, because some of these lesions can be misinterpreted and are finally deemed to be Bosniak IIF lesions. Secondly, most of the progressions occur within a time frame of 4 years [9,12,18,19]. In one of the largest studies of Bosniak IIF CRCM, at a mean follow-up of 20 months, only 14 cases (7%) showed evidence of progression to stage III, with a mean (range) time to progression of 11 (3–65) months [20]. Hindman et al. [9] showed that 10.9% (17 of 156) Bosniak category IIF cystic lesions progressed to malignancy, and progression occurred within 0.5–3.2 years. Generally, the outcomes for the Bosniak IIF category demonstrated clinical reliability by a low rate of radiological progression.

According to the recommendations of the American College of Radiology it may be practical to propose imaging with CT/MRI at 6 and 12 months after initial examination and yearly thereafter for a total of 5 years [9,15,16,18,21,22]. To date, there are no straightforward national or international guidelines that recommend how intense, long and which modality is optimal for the patient with a Bosniak IIF lesion under a surveillance strategy. Both the European Society of Radiology and the European Association of Urology (EAU) recommend a similar follow-up protocol and are mainly based on expert opinion.

Our policy is to follow Bosniak IIF lesions with CT every 6 months during the first 2 years and then annually. Based on our present data, we feel that the number of CT scans could be reduced. Additionally, we suggest performing at least one MRI during follow-up, especially in the early phase at ≤ 4 years. To evaluate the true nature of CRCM, we feel it necessary to form and provide data with a 10 year follow-up. With our present proposed flow chart a patient will undergo five CTs and one MRI during that period. CEUS could be another optional alternative. The rationale and reason for why we feel this to be appropriate, are as follows: i) the overall low incidence of cancer in the general Bosniak IIF population; ii) the vast majority are low stage/grade tumours; iii) a significant proportion are cystic RCC variants that have a favourable prognosis; iv) most of the solid RCCs presented as CRCM lack aggressive

features on final pathology; v) those with unfavourable histology can potentially be discerned in the early phases. Discerning the true incidence of cancer in the Bosniak IIF category is problematic, as few lesions undergo surgery and urologist can only report malignancy rates in a very limited patient population (mostly those who progress). However, it is far more appropriate for the general urological community, to count and consider remaining stable cysts as benign, as the vast majority will never undergo surgery.

Graumann et al. [22] proposed follow-up by US and MRI after initial CT characterisation. The recognised rate of interobserver variation on CT has been shown for MRI as well [14]. MRI has a higher contrast resolution than CT, which could potentially lead to lesion upgrading or downgrading. Conversely, the disadvantage of MRI is the detection of calcifications. Israel et al. [23] showed and previously described, that lesions can be re-classified according to the presence of calcifications up to the Bosniak IIF category. When we detect calculi in the cystic lesion, CT should be the preferred imaging method. When the lesion is still not easy to classify or has some worrisome features, MRI should be proposed thereafter. In those patients, who cannot undergo CT studies, one should rely on US combined with MRI thereafter. Because according to the calcification score the lesion cannot be upgraded into the surgical category. Especially in the younger patient population, increasing radiation risks due to longer follow-up merit stronger consideration of MRI surveillance or CEUS (when available).

According to the BCS, IIF cysts are potentially malignant and should be followed with CT examinations, to determine and detect early progression in size, intracystic changes or to determine contrast enhancement patterns resulting in an upgrading. This strategy may be varied when the age, history of RCC, presence of ipsilateral or contralateral suspicious RCC, and comorbidity of the patient are considered [24]. These risk factors were initially evaluated by the Cleveland Clinic team for the Bosniak III category. In our opinion, it is logical to consider these factors as a trigger for intervention in patients (especially at younger ages) with Bosniak IIF lesions as well. Although clinical data on this particular topic are lacking, and age thresholds have never been proposed. Progression in complexity but not in size appears to be the most important indication of malignancy. However, rapid size progression should be a trigger to consider surgery as well. Not surprisingly, in the present study we did not find any progression into locally advanced disease, metastatic spread, or other unexpected oncological sequelae, which strongly corresponds with the current literature [9,12,15,16,18].

According to the 2014 EAU Guidelines on RCC, Bosniak III cysts should be regarded as RCC [11], but surgery may be an overtreatment in a significant propor-

tion of cases. Recently, we suggested our treatment strategy for these lesions [12]. Bosniak III lesions deserve further evaluation with MRI or CEUS and consideration of concomitant factors before recommending surgery [12,24]. We think there is more room for debate than previously thought. Bosniak IV renal cysts are considered as malignant lesions, the overall incidence of RCC was almost 80%, with 19% being high-grade lesions in our present patient population. These results underscore that surgical resection is an appropriate management strategy. Active surveillance may be an alternative management option in patients with significant co-morbidity, similarly to solid tumours, and probably we should offer these patients only US, otherwise equivocal CT/MRI results may negatively impact our asymptomatic patients (Fig. 2). We are fully aware, that clear data on this are lacking.

The present study has several critical limitations. The sample size is relatively small for each Bosniak category, in order to address such a complex protocol. The study design was retrospective, and the sample size was limited. We included only lesions with > 3 years follow-up, in order to evaluate mid-term outcomes, thus introducing selection bias. Another major limitation is that we did not evaluate the intra- and interobserver variability. However, this updated study reflects the real clinical scenario with its known common diagnostic flaws and biases. We are fully aware that long-term data are lacking and therefore further conclusions with regard to the natural history may be speculative. Over the last decade there has been a change in CT and MRI technologies, which we did not address and further analyse. MRI has a superior contrast resolution compared to CT, which may lead to up- or downgrading in Bosniak category, especially in less experienced hands [5,9,19]. We were able to show the importance of MRI correlation to CT but only in a very small subset of cases. The role of CEUS was not addressed in our present analysis, nevertheless according to the recent literature, CEUS can reveal the intracystic structure of the lesion better than CT/MRI [7,25]. In addition, CEUS can alleviate the expense, time and potential nephrotoxicity of MRI, and thus should be further studied and included in management schemes, especially for surveillance strategies.

We think that our mid-term follow-up data enable us to suggest a management strategy for daily clinical care. We also acknowledge that the proposed scheme is partially subjective, based on our clinical work and evidence-based literature. The protocol should be prospectively evaluated and requires further scientific validation.

Conclusion

The BCS is useful for clinical decision-making and has proved its efficacy over three decades. Uncertainties

remain due to overlaps between the Bosniak IIF and III categories. However, there is still room for improvement in study reporting and diagnostic criteria in the Bosniak IIF and III categories. An individualised decision-making is necessary in a certain proportion of patients. Our decision-making tool may be useful for daily clinical care, but needs further testing.

Conflict of interest

The authors declare no conflict of interest.

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