Evaluation of Complex Renal Cysts by Contrast-Enhanced Ultrasound and Microvascular Flow Imaging

PhD thesis

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2025

Introduction

In routine radiological practice, complex renal cysts are most commonly encountered as incidental findings during cross-sectional imaging or ultrasound examinations. The Bosniak classification system, widely used for their characterization, provides guidance on assessing the likelihood of malignancy in these lesions. As the complexity of a renal cyst increases (from a simple cyst to a cystic tumor) the probability of malignancy rises correspondingly.

Even for malignant lesions, however, distinguishing between different grades of malignancy remains important. Many of these tumors are slow-growing and non-metastatic, making precise classification essential, particularly in cases where surgical intervention may be contraindicated. Such contraindications might include a solitary kidney, advanced age, significant comorbidities, or pre-existing renal insufficiency. Based on the PADUA scoring system, lesions that are predominantly centrally located, may require radical nephrectomy further expanding the range of relative contraindications. Alternative treatment options for these small renal masses, which do not exceed 4 cm in size, include active surveillance, various interventional radiology techniques such as radiofrequency ablation, cryoablation, and stereotactic external radiation therapy. Under these circumstances, accurate grading of potentially tumorous lesions can serve as a decisive factor in clinical decision-making.

The Bosniak classification system was originally developed for evaluation using computed tomography (CT). While the system has undergone modifications and adaptations for contrast-enhanced ultrasound (CEUS), both our clinical experience and the existing literature suggest that the correlation between imaging findings and the pathological features of surgically resected lesions remains suboptimal. This limitation highlights the need for continued refinement in the imaging-based assessment of complex renal cysts to enhance diagnostic accuracy and guide clinical management.

The Bosniak Classification System for Renal Cystic Masses in Contrast Enhanced Computed Tomography

The Bosniak classification system, a pivotal tool in the assessment of renal cystic masses, has undergone significant refinement since its inception. The original classification, now termed Bosniak v2005, stratifies renal cystic lesions into five categories based on their imaging characteristics observed on contrast-enhanced computed tomography (CECT). This system has been instrumental in estimating malignancy risk and guiding decisions regarding follow-up or intervention. Recently, an updated version, Bosniak v2019, has been introduced, gradually gaining prominence in clinical practice.

Radiologists and urologists widely employ the Bosniak classification as a standard for evaluating renal cystic masses. Bosniak v2005, the previous benchmark, has been cited extensively in clinical guidelines and remains in use in certain regions. However, the introduction of Bosniak v2019, which incorporates separate criteria for CECT and magnetic resonance imaging (MRI), reflects advancements in imaging modalities and clinical understanding.

Adoption of Bosniak v2019 varies globally. The 2022 European Association of Urology Guidelines and Canadian Urological Association Guidelines reference Bosniak v2019, while the 2021 American Urological Association

Guidelines continue to rely on Bosniak v2005. This variability highlights an ongoing transition period between the two versions.

The role of ultrasonography in applying the Bosniak classification remains a topic of debate. Historically, ultrasound was considered unsuitable for characterizing Bosniak categories due to its inability to reliably demonstrate neovascularization, a key feature identified by contrast-enhanced CT or MRI. However, recent advances in contrast-enhanced ultrasound (CEUS) challenge this notion, with studies suggesting improved sensitivity for detecting enhancing intralesional septa and soft tissue components compared to both CT and MRI. Despite these promising findings, CEUS remains supplementary and is not universally accepted as a standalone imaging modality for Bosniak classification regarding the poor availability of this specific modality.

The Bosniak system assigns categories using Roman numerals. Notably, Bosniak v2019 transitioned from the term "category" to "class." Therefore, from now on, the term Bosniak class will be used. The recent classes are defined as follows:

Bosniak I

- Characteristics: Simple, benign cyst with thin walls (≤2 mm), water density, no septa, calcifications, or solid components, and no enhancement. Management: No follow-up required. Malignancy risk: ~0%.

Bosniak II

- Characteristics: Minimally complex cysts with thin (<1 mm) septa or calcifications, perceived enhancement, or non-enhancing high-attenuation lesions (<3 cm). Management: No follow-up required. Malignancy risk: ~0-6%.

Bosniak IIF

- Characteristics: More complex cysts with multiple thin septa, minimally thickened walls, or calcifications that may be thick and nodular. High-attenuation lesions (>3 cm) without enhancement. Management: Periodic imaging follow-up (e.g., US, CT, or MRI at intervals over 5 years). Malignancy risk: ~5-26%.

Bosniak III

- Characteristics: Indeterminate cystic masses with thickened, irregular, or smooth walls/septa and measurable enhancement. Management: Surgical intervention (partial nephrectomy) or radiofrequency ablation for patients unsuitable for surgery. Malignancy risk: ~55-72%.

Bosniak IV

- Characteristics: Clearly malignant cystic masses, meeting Bosniak III criteria with the addition of enhancing soft tissue components. Management: Partial or radical nephrectomy. Malignancy risk: ~91-100%.

The system is named after Dr. Morton A. Bosniak (1929-2016), a renowned radiologist and professor emeritus at New York University Langone School of Medicine. First introduced in 1986, the Bosniak classification has evolved through several iterations, with major revisions in 1993, 1997, 2005, and 2019. The introduction of category IIF in 1993 was particularly notable for enhancing the system's clinical utility by stratifying intermediate-risk lesions.

The Bosniak classification remains a cornerstone in the evaluation of renal cystic masses, enabling clinicians to estimate malignancy risk and tailor management strategies. As imaging technology and techniques advance, updates such as Bosniak v2019 continue to refine diagnostic accuracy and clinical applicability. However, challenges in

standardizing the system across imaging modalities and regions underscore the need for further research and consensus-building efforts.

Bosniak Cyst Classification: Scoring Criteria on Multiparametric Ultrasound

The Bosniak classification system has been adapted for ultrasound, with notable variations compared to the original computed tomography based criteria. As not only the CEUS but conventional ultrasound findings are considered, it is favourable to use the term of multiparametric ultrasound when speaking of US assessment of complex renal cystic lesions. While simple renal cysts (class I) and certain minimally complex cysts (class II) are primarily assessed with B-mode US, complex renal cysts often require characterization via CEUS.

The following list details the principles of the CEUS-adapted Bosniak classification based on its criteria and the resulting categorization. The classification categories remain unchanged; however, it does not address the correlation of US/CEUS findings with cross-sectional imaging. It is important to note that the morphological features described below do not always correspond to those identified on cross-sectional imaging. The primary reason for this discrepancy is the higher resolution of ultrasound examinations, which enables classification based on finer details, such as wall and septal irregularities.
The enlisted criteria synthesize findings from multiple studies and provide a framework for US-based Bosniak scoring. Summary of the multiparametric US criteria, developed in accordance with the recommendations of European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB):

Class I: Simple Benign Cysts

- Thin wall (<2 mm), sharp margins, absence of irregularities or calcifications, anechoic content, and posterior acoustic enhancement. Fully evaluated as benign on B-mode US; no use of ultrasound contrast agents (UCA) is required.

Class II: Minimally Complex Benign Cysts

- Cysts meeting simple cyst criteria but with 1–3 thin septa (<2 mm) without irregularities. Wall and/or septal calcifications that do not obscure cystic content. Internal debris, echogenic content, or a mixed appearance, provided no enhancement is seen on CEUS. Limited microbubble presence detected in the wall or septa during CEUS. Benign lesions identified on B-mode US. UCA administration is optional but may show individual microbubbles within thin septa or the wall.

Class IIF: Presumably Benign, Imaging Surveillance Advised

- Multiple thin septa or minimally thickened (2–3 mm) smooth septa and borders. Internal debris, echogenic/mixed content, or calcifications that slightly impede the evaluation of cystic structures. Completely intrarenal cysts meeting class II criteria where differentiation between enhancing and non-enhancing walls or borders is unclear.

Class III: Indeterminate Lesions

- Enhancing smooth thick walls (≥4 mm) or septa. Enhancing irregular walls (>3 mm) or septa. No associated nodular components. These lesions remain indeterminate and typically require surgical evaluation.

Class IV: Likely Malignant Cystic Tumors

- Features of category III cysts combined with enhancing soft tissue protrusions. Nodules with obtuse margins (≥4 mm) or acute margins of any size. These lesions are considered highly suspicious for malignancy and warrant definitive treatment, such as partial or radical nephrectomy.

Contrast-Enhanced Ultrasound

CEUS can be regarded as an extension of conventional and Doppler ultrasound by visualizing the vasculature of the examined region or lesion. Not only the large calibre vessels, but the microvasculature can be assessed, including the parenchymal capillaries. Parenchymal enhancement can be perceived by contrast enhanced cross-sectional modalities, but CEUS allows better identification due to the high temporal (direction of in parenchymal small vessels) and spatial resolution (distinction of small vessels).

Therefore, more detailed information of the vasculature and enhancement is given of the target by contrast-enhanced ultrasound resulting in higher sensitivity compared to cross-sectional imaging. This increased sensitivity can be a game changer in the characterization of complex renal cysts as the better spatial resolution allows detection of fine vascularization in tiny structures like thin septa or small intralesional soft tissue components.

Ultrasound Contrast Agent

SonoVue® (sulphur hexafluoride microbubbles), developed by Bracco, is a second-generation ultrasound contrast agent (UCA) designed to enhance ultrasound imaging across a wide range of applications, including vascular and non-vascular imaging.

SonoVue® consists of microbubbles containing sulphur hexafluoride (SF_6), an inert gas with high echogenicity, stabilized by a phospholipid monolayer. The average microbubble diameter is 1–10 microns, ensuring that they remain within the vascular space without crossing the endothelial barrier. As there is no penetration of the UCA to the extravascular spaces SonoVue® is a purely intravascular contrast agent, all contrast signal at any point during the exam is of vascular origin – contrasting small molecule CT/MRI contrast agents.

Physics

- Echogenicity: The high acoustic impedance mismatch between the gas core and surrounding tissues generates strong backscatter, enhancing the ultrasound signal.
- Resonance behavior: Microbubbles oscillate when exposed to an ultrasound field. Their non-linear oscillations produce harmonic frequencies, improving contrast resolution and enabling contrast-specific imaging techniques such as harmonic imaging or pulse inversion.
- Biostability: The phospholipid shell enhances the stability of microbubbles, allowing them to persist in the bloodstream for several minutes post-injection, enabling adequate imaging time.
- Safety Profile: Sulphur hexafluoride is rapidly eliminated via the lungs, minimizing systemic toxicity. The gas is biologically inert and does not interfere with metabolic processes.

Mechanisms of Distribution

Upon intravenous injection, SonoVue® distributes rapidly within the vascular compartment. The following mechanisms govern its behavior in the body:

- Intravascular Retention: The size of the microbubbles restricts them to the bloodstream, providing pure intravascular contrast. This property is critical for evaluating perfusion, vascular integrity, and dynamic flow patterns.

- Microcirculation Imaging: The ability of microbubbles to traverse capillaries (diameter of 1-10 microns) enables the assessment of tissue perfusion at the microvascular level, making it valuable in detecting ischemia or tumor neovascularization.
- Real-Time Dynamics: The contrast agent's distribution can be observed in real-time, offering dynamic information about blood flow and perfusion kinetics.
- Clearance: SonoVue® microbubbles are removed from circulation primarily by physical dissolution of the gas and exhalation via the lungs. The lipid shell components are metabolized naturally.

Summary and Literature Review

Value of Contrast-Enhanced Ultrasound and Microvascular Flow Imaging in the Characterization of Complex Renal Cysts

Contrast-enhanced ultrasound (CEUS) is increasingly employed for the characterization of renal lesions, including complex cysts. Since many of these lesions are detected incidentally, CEUS has gained popularity due to its lack of ionizing radiation, widespread availability, and high temporal and spatial resolution. The Bosniak classification system, originally developed for assessing cystic renal lesions on CT, has since been adapted for use with MRI and CEUS. CEUS has demonstrated comparable performance to CT and MRI in characterizing complex cystic renal lesions, and it has also shown the ability to upgrade a significant number of lesions. The most commonly used contrast agent for CEUS (SonoVue/Lumason) remains entirely intravascular, unlike CT and MRI contrast agents, which permeate the extracellular space. This intravascular nature of CEUS contrast enhances purely vascular signals, providing superior temporal and spatial visualization of intracystic vascularity. CEUS has proven particularly effective in the follow-up of equivocal cystic lesions, such as Bosniak IIF cysts, whereas monitoring with CT results in significant cumulative ionizing radiation exposure for patients.

According to current guidelines, Bosniak III and IV lesions are considered candidates for surgical resection, making these categories the primary ones where histopathological correlation is feasible. While a diagnosis of Bosniak IV has been shown to be highly specific for malignancy, a significant proportion of Bosniak III lesions are benign tumors or pseudolesions, with the prevalence of malignancy varying widely across studies. It has also been shown that CEUS tends to assign a higher classification stage than CT or MRI. As a result, there has been a recent shift toward surveillance of Bosniak III cystic lesions, given that approximately 50% of surgically excised lesions in this class are benign. This shift is particularly important for patients with chronic kidney disease and significant comorbidities, which increase the risks associated with invasive management.

Biopsy of cystic renal lesions carries risks such as potential hemorrhage, tumor tissue spread, and the internal heterogeneity of these lesions often leads to biopsy samples that are not representative of the final histopathological diagnosis. Therefore, current guidelines do not recommend biopsy unless a substantial solid component (Bosniak IV morphology) is present. Consequently, the selection of surgical candidates relies predominantly on non-invasive imaging techniques. As such, correlating imaging classification with histopathological diagnosis is crucial to accurately assess the real-world performance of these techniques.

Despite advancements in imaging, non-contrast ultrasound remains one of the primary methods for the initial detection of renal lesions, particularly in settings outside major academic centers, where it is far more accessible than CEUS. As a result, there remains an unmet need for evaluating the vascularity of such lesions without the use of

ultrasonic contrast agents. Unfortunately, color and power Doppler ultrasound lacks the sensitivity to detect small-caliber vessel flow, making it inadequate for reliably assessing vascularity within, for example, the septa of complex cysts. Consequently, the diagnostic performance of conventional ultrasound is significantly lower than that of CEUS in characterizing complex renal cystic masses.

Recent advancements in ultrasound technology, such as microvascular flow imaging MVFI, have substantially improved the sensitivity of non-contrast vascular imaging. This is achieved primarily through the more selective suppression of clutter and motion-derived artifacts. These improvements allow the visualization of smaller-caliber vessels, providing new opportunities to assess microvasculature within renal lesions without the need for contrast agents. Several studies have already demonstrated the increased sensitivity of MVFI for detecting slow flow and flow within small vessels across various tumor types.

It was recognized early on that the addition of ultrasonic contrast media could enhance conventional color-Doppler ultrasound (CDUS) for assessing renal lesions. However, with the advent of low mechanical index CEUS presets and more stable contrast agents, this approach was quickly phased out. Recent studies suggest that MVFI can also serve as an ancillary tool following the administration of ultrasound contrast agents, known as CE-MVFI. It is important to note that CEUS does not directly depict blood flow but instead visualizes resonating microbubbles of contrast agent—whether stationary, adherent, or moving within vessels. Therefore, CE-MVFI theoretically offers added value by combining the increased sensitivity of MVFI for small vessel flow with the enhanced contrast provided by microbubbles.

We aimed to assess the performance of non-contrast MVFI imaging in comparison to CEUS, while also exploring the potential applications of CE-MVFI. Additionally, we address some of the technical challenges and specific artifacts encountered during pre- and post-contrast evaluation of renal masses and cystic lesions.

Goals

We aimed to evaluate the CEUS imaging characteristics and outcomes for Bosniak III and IV lesions, as these are candidates for resection and allow for histopathological correlation. Additionally, we aimed to assess the positive predictive value (PPV) of CEUS within these subcategories and analyzed the histological diagnoses of true and false positives. Furthermore, we conducted a retrospective re-evaluation of cases where CEUS findings were discordant with the final histopathological outcomes.

Our other objective was to assess the performance of non-contrast MVFI imaging in comparison to CEUS, while also exploring the potential applications of CE-MVFI. Additionally, we address some of the technical challenges and specific artifacts encountered during pre- and post-contrast evaluation of renal masses and cystic lesions.

Materials and Methods

Radiological Findings and Pathological Correlation of Bosniak III-IV Cystic Renal Lesions

We conducted a retrospective review of all renal CEUS examinations at our center from January 2019 to January 2022. CEUS diagnoses were extracted from reports, and dominant B-mode and CEUS features, including lesion size, depth, and vascularity, were analyzed from both single images and cine recordings. The arterial phase was

documented using cine loops. Histopathological reports were also reviewed, considering benign lesions like oncocytoma and multilocular cystic renal neoplasm of low malignant potential (MCRNLMP) as concordant diagnoses, while simple and hemorrhagic cysts, along with localized cystic kidney disease, were deemed discordant.

Contrast-Enhanced Ultrasound Exam Technique

CEUS examinations were supervised by two experienced radiologists (Dr Ákos Járay, Dr. Péter Farkas), each with over 10 years of expertise. The procedures utilized one of two high-end ultrasound scanners: Samsung RS85 with CA1-7A probe or GE Logiq E10 with C1-6 probe.

Each CEUS examination was preceded by a B-mode assessment, followed by color-Doppler and/or microvascular flow imaging. The contrast agent SonoVue® (Bracco, Milan, Italy) was administered intravenously as a bolus of 1.2-2 ml, followed by 10-20 ml saline. Timing commenced upon completion of the contrast injection. All studies were electronically documented, with cine loops recorded during the early arterial phase. CEUS exams were performed using a low mechanical index (0.069-0.07) and split-screen display. The assessment of B-mode morphology (including septal thickness, complexity, internal solid nodules, and wall irregularity) and CEUS features (enhancing internal nodularity or septa) contributed to the up-to-date Bosniak classification.

Microvascular Flow Imaging

Another retrospective study was conducted between September 2019 and March 2020, following relevant guidelines and regulations.

A total of 92 patients were evaluated for newly discovered complex cystic renal lesions. All underwent non-contrast evaluation prior to CEUS, with 10 cases not receiving CEUS due to follow-up of confirmed lesions or non-necessity after non-contrast exams. The reported Bosniak class in the CEUS report was considered the gold standard. Retrospective assessments of MVFI, CE-MVFI, and color-Doppler categorization were performed. MVFI was documented in 28 of the 92 cases, utilizing either split screen or overlay display. color-Doppler and MVFI assessments were conducted in 13 patients, while both pre-contrast and CE-MVFI were done in 16 cases. A summary of MVFI categorization compared to CEUS was presented. By the time of the evaluation, 7 patients had undergone surgical treatment.

Contrast-Enhanced Ultrasound and Microvascular Flow Imaging Exam Technique

All CEUS exams were supervised by the aforementioned radiologists, using the same Samsung RS85 ultrasound scanner with a CA1-7A transducer. Each CEUS was preceded by thorough B-mode evaluation, followed by color-Doppler and/or MVFI assessment. The contrast agent SonoVue® (Bracco, Milan, Italy) was administered intravenously as a bolus of 1.2-2 ml, followed by a 10-20 ml saline, with a timer started at the end of the injection. Studies were electronically documented, with cine loops recorded during the early arterial phase and later phases followed with interval scanning to reduce microbubble destruction. CEUS exams were performed at a low mechanical index (0.069-0.07) using a split-screen display. Factors such as septal presence and complexity, internal echogenic content, wall thickening, calcifications, and solid internal nodules contributed to the final CEUS Bosniak class, as reported previously. CE-MVFI assessments were conducted in several cases, but only after the formal CEUS exam during the late venous phase.

B-mode ultrasound served as the baseline investigation for all examinations, providing information on the location, size, and morphology of renal lesions. Color-Doppler ultrasound (CDUS) offers additional details regarding renal and intralesional vascularity, indicating the direction of blood flow through color coding. During microvascular flow imaging (MVFI), careful probe positioning is essential to minimize motion artifacts and allow visualization of the fine vasculature. Although this technique is highly sensitive, it is not color-coded. In contrast-enhanced ultrasound (CEUS) examinations, tissue signals are suppressed, allowing only the microbubble signals to be visualized during contrast.

Statistical Analysis

All stored images, cine recordings, and the reports were retrospectively reviewed by two of the authors during the study in a non-blinded fashion, final assessment was based on consensus. As the originally assigned Bosniak class defined further management, this was not altered. In patients with multiple lesions only the one with the highest Bosniak class based on CEUS was included in the study. Histopathological data and images were reviewed with the aid of a board-certified pathologist with experience in the assessment of kidney malignancies (Dr. Dávid Semjén).

95% confidence intervals (CI) of dichotomous categorical values were determined with the GraphPad QuickCalcs calculator using the modified Wald method. Fisher's exact test was used to assess the significance for categorical diagnoses. Continuous variables were assessed using unpaired t-test with the GraphPad Prism software. In all cases $P < .05$ was determined as being significant.

Comparisons between CEUS, MVFI and CDUS were conducted using Fleiss' kappa statistic, relative sensitivity by Fisher's exact test. Quantitative results (lesion size and depth) were compared using unpaired t-test.

Results

All patient records and referral for renal CEUS (n = 536) were reviewed between 2019 and 2022. In total 58 lesions had a diagnosis of Bosniak III or IV class in this period. After removal of duplicates and non-contrast follow-up exams where no CEUS was conducted 50 lesions (in 49 patients) were selected for further evaluation. Among these 31 patients had surgery or biopsy with histopathological assessment.

B-Mode and Contrast-Enhanced Ultrasound Morphology of Bosniak III and IV Lesions

We have found no difference regarding size and depth of Bosniak III and IV lesions. Among dominant imaging features, thin enhancing septa were significantly more common in Bosniak III lesions ($P = .0004$), while intracystic solid nodularity was the exclusive feature of Bosniak IV lesions ($P < .0001$).

Color-Doppler and Microvascular Flow Imaging Compared with Contrast-Enhanced Ultrasound

Given that we conducted a retrospective data analysis, results for colour Doppler and MVFI measurements were not always available, as the routinely performed and unequivocally more sensitive CEUS examinations replaced these techniques. However, the number of cases in which colour Doppler and MVFI examinations were performed allowed for a comparison of these methods with the MVFI technique in terms of sensitivity.

CDUS was performed less commonly than MVFI, and the latter had a significantly higher agreement with CEUS regarding the visualization of lesion vascularity ($P = .0199$, Table 1).

	CDUS (n = 16)	MVFI (n = 24)
Vascularity visualized (n)	2 (12.5%)	12 (50%)
PPV	12.5%	50%
95% CI	0.02–0.37	0.31–0.68

Table 1

Performance of color-Doppler Ultrasound (CDUS) and Microvascular Flow Imaging (MVFI) Compared With CEUS

Histopathological Results

A substantial number of patients had no further record in our electronic health system. Since this is a tertiary referral center, it can be assumed that many of these are not truly lost to follow-up, rather their further management continued in the referring center. Partial nephrectomy was the primary method of operative management for both Bosniak III and IV lesions, whilst radical nephrectomies were predominantly performed to resect Bosniak IV lesions.

Among the diagnoses, clear cell renal cell cancer (ccRCC) was more common among Bosniak IV lesions (P = .029). Among RCC-s Fuhrman grade was assessed in 14 cases of ccRCC/RCC. Eight lesions (57.14%) were Fuhrman grade of 1. Two lesions (14.28%) had a Fuhrman grade of 1–2. A single case had a Fuhrman grade of 2 and 1–3, respectively.
After stratifying histopathological diagnoses into benign vs malignant, Bosniak IV lesions were found to be strongly associated with malignancies (P = .0002).

Among the patients classified as having Bosniak III or IV complex renal cysts based on CEUS assessment, histopathological evaluation was performed in 31 cases following biopsy, partial, or radical nephrectomy. In 14 cases, this may have been due to the fact that, although the diagnosis was made at our institution, the therapeutic management was carried out at another hospital. In five cases, despite the lesions being deemed malignant, the urology team opted for follow-up instead of immediate intervention. This decision may have been influenced by the patient's overall condition, comorbidities, or age.

Comparison of Histopathological and Contrast-Enhanced Ultrasound Classification

The positive predictive value (PPV) and its 95% CI for all lesions, and Bosniak III and IV lesions were separately summarized. We have found that the PPV of a Bosniak IV diagnosis considerably exceeded that of a Bosniak III one. Predictive power for true lesions was comparable in both categories (P = .33); however, the predictive power for a malignant histopathological outcome was significantly greater (P = .0002) for Bosniak IV lesions. Mean size and depth of malignant, benign, and non-neoplastic lesions, as well as the age of respective patients did not differ significantly.

Of the patients involved 59.7% (55/92) were male, and 40.2% (37/92) were female. The median age was 67 years. The median size of the investigated renal lesions was 25 mm (range: 3–147 mm). Lesions were categorized based on the most defining B-mode imaging features, showing that thin septation (21 cases), solid masses (18 cases), and intracystic solid content were the most common findings on non-contrast ultrasound imaging. The reported formal Bosniak class of the lesions showed that the majority fell into the Bosniak II (22 cases), Bosniak IIF (17 cases) group, followed by enhancing masses and the Bosniak I cyst (12 cases each) class.

Distinguishing between Bosniak II and Bosniak IIF subgroups can be challenging, as the differences are often subtle. In daily clinical practice, the most prudent approach (which we followed) is to classify lesions that do not fully meet the exact criteria for either Bosniak II or Bosniak III categories as Bosniak IIF.

Comparison of Microvascular Flow Imaging to Contrast-Enhanced Ultrasound in the Assessment of the Renal Lesion Vascularity

In 28 cases were MVFI and CEUS simultaneously performed and documented sufficiently to allow retrospective categorization based on the previously defined criteria. In these cases Fleiss' kappa statistic was used to assess agreement between CEUS and MVFI. Overall weighted kappa index was found to be 0.806 indicating substantial consistency between the methods by the Landis-Koch scale. In 6 cases were results discordant, and in all of these CEUS upgraded the class of the lesion (4 lesions to Bosniak IIF, 2 lesions to Bosniak III).

We have evaluated relative sensitivity of MVFI with the same benign vs. malignant categorization, using the formal CEUS diagnosis considered as a gold standard, with Fisher's exact test, which demonstrated a good sensitivity and specificity.

	Value	95% CI
Sensitivity	0.75	0.40-0.95
Specificity	1.0	0.83-1.0
Positive predictive value	1.0	0.60-1.0
Negative predictive value	0.90	0.72-0.98
p<0.0001 (Fisher's exact test)		

Table 2

Relative sensitivity, specificity and predictive value of MVFI compared to CEUS.

Histopathological Results

Only 7 lesions that were evaluated with both CEUS and MVFI went under resection by the time of the study. Among the resected lesions one was found to be a benign tumor (oncocytoma) during histopathological assessment, whilst the rest proved to be different subtypes of renal cell carcinoma. It has to be emphasized that many patients were referred by external centers, thus the actual number of operated lesions is likely to be higher (the authors only had authorized data collection requests to the local electronic health records).

Microvascular Flow Imaging and Color-Doppler Imaging Compared to the Contrast-Enhanced Ultrasound Diagnosis

Within the study period 13 lesions have been documented to undergo both CDUS and MVFI imaging at the time of the CEUS exam. Among these lesions MVFI showed a superior (substantial) agreement with the CEUS exam in contrast to CDUS (slight agreement) demonstrating a better correlation with the CEUS diagnosis, and substantially lower number of discordant diagnoses (Table 3).

	color-Doppler	MVFI
Kappa	0.158	0.678
SE of Kappa	0.107	0.157
95% CI	-0.05-0.36	0.37-0.98
Weighted Kappa	0.133	0.77
Landis-Koch agreement scale	Slight agreement	Substantial agreement
Discordant diagnoses/total	9/13	3/13

Table 3

Agreement between CEUS and color-Doppler and MVFI respectively for lesions that were evaluated with all methods.

Discussion

Bosniak III and IV Cystic Renal Lesion Categorization Using Contrast-Enhanced Ultrasound

In this study, we have found a high positive predictive power of CEUS for the final histopathological grade of Bosniak IV lesions, with a considerable decrease among Bosniak III lesions owing to a large number of non-neoplastic and benign mimickers.

Previous studies either conducted a pooled analysis of cystic and solid renal lesions in this regard, or relied on surrogate techniques rather than direct histopathological correlation. We have found that Bosniak III lesions have a high likelihood to represent either a non-neoplastic lesion, or a tumor with low malignant potential. The Bosniak classification has been used widely for the characterization of cystic renal lesions, first on CT, then later adapted for MRI and CEUS as well. Nonetheless, it has been also known that cystic lesions are generally overcalled, leading to unnecessary resections of benign and borderline malignant lesions. It is also known that even if malignant, cystic renal lesions are typically more indolent, than their solid counterparts. This is also supported by the low Fuhrman grade observed in the resected cystic ccRCC-s in our study.

It has been shown by a recent meta-analysis that the effectiveness of the Bosniak classification system is particularly weak for the Bosniak III class, resulting in 49% of lesions being overtreated. The estimated surgical number of Bosniak III lesions that need to be treated to avoid a single case of metastatic disease also stands very high at 140. Our study is in line with prior evidence, showing that predictive power drops considerably for Bosniak III lesions, and active surveillance may benefit many of these patients rather than early surgical treatment.

Some studies have shown that contrary to its robust sensitivity and high negative predictive power, CEUS also has a lower specificity and positive predictive value compared with CT/MRI in the evaluation of complex cystic renal lesions. On the other hand, different studies have found CEUS to have a comparable diagnostic performance in assigning a Bosniak class. It has been shown recently that only 17% of the Bosniak III class lesions characterized by CEUS in addition to cross-sectional imaging are truly malignant which is comparable to the 25% proportion found in our study. To improve the predictive power some studies have investigated lesions size and demographic parameters to make better clinical prediction models for assessing the malignancy risk of this group, but the added benefit was found to be slight. These and our results underline the need for more cautious surveillance strategy particularly for Bosniak III

class lesions, especially as cancer-specific survival rate in this group was found to be excellent. Furthermore, patients with Bosniak III lesions were found to be significantly younger in our study. In summary, CEUS definition of Bosniak III vs Bosniak IIF lesions needs to be more clearly defined to increase specificity.

Vivid enhancement within relatively thin septa could be ascertained as a key common denominator of false positive results. It underlines the importance of morphological correlation. It has been proposed that septal enhancement accompanied by nodularity is a strong predictor of malignancy, and is considered as one of the primary rule-in criteria of Bosniak IV lesions. It has to be also emphasized that some benign tumors such as oncocytoma and MCRNLMP are virtually impossible to differentiate using noninvasive imaging, and as a result represent a currently unresolved diagnostic challenge. In our study all lesions where the dominant feature was thin but vividly enhancing septa were found to be either low-grade tumors or non-neoplastic lesions. This underlines the importance of the adoption of conservative CEUS Bosniak classification standards.

In this study, we have found a robust increase in sensitivity using non-contrast MVFI rather than CDUS for detecting internal vascularity within cystic renal lesions. Further prospective studies are needed whether non-contrast, MVFI-assisted follow-up of cystic renal lesions is a safe alternative in select cases.

Histopathological correlation was only available for the majority, but not for all Bosniak III and IV lesions, which could represent selection biases, and forms a limitation of the present study. A further important limitation to the present study is caused by a “known unknown,” namely the number of true and false negatives. This does not allow the assessment of factors such as sensitivity, specificity, and negative predictive value. As there is no surgical or biopsy indication for cystic renal lesions having a Bosniak grade I–IIF there is no approach to overcome this limitation. Previous attempts to use another non-invasive imaging technique (CT or MRI) as a surrogate suffer from another important limitation, as true vs false positivity becomes less clearly defined and subject to the inherent biases of another imaging modality. Another important limitation is posed by the study period, partially predating the recently published EFSUMB position statement. As a result several lesions with relatively thin but vividly enhancing septa have been classified as Bosniak III lesions as mentioned earlier. Vivid septal enhancement was suggested as a potentially high-risk feature by earlier studies. More recent evidence and the above-mentioned EFSUMB position statement have, however, adopted a more conservative approach, requiring associated septal nodularity and/or significant septal thickening, as indicators of a potentially malignant lesion. Nonetheless, as pointed out by a very recent review, the line between profound septal enhancement and sporadic microbubbles, and thus a diagnosis of a Bosniak IIF or III lesion remains extremely narrow. Our findings are in agreement with this paradigm shift, and also underline the need for rapid and widespread adoption of these recommendations. Future studies will be needed to determine whether a measurable improvement in predictive power can be observed as a result.

Altogether our results show that while CEUS Bosniak IV classification carries a very high predictive power for malignancy, a substantial number of surgically treated CEUS Bosniak III lesions are either benign or non-neoplastic lesions. More surveillance-oriented management of these patients would be beneficial.

Microvascular Flow Imaging in the Assessment of Cystic and Solid Renal Lesions

We have shown that MVFI outperforms conventional color-Doppler imaging in the characterization of renal lesions when compared to CEUS as a gold standard. In our study the performance of MVFI was particularly lower for lesions where vascularity is subtle/equivocal (notably Bosniak IIF cysts). CEUS with its superior ability to depict trickle-like

flow of occasional microbubbles within the internal septations of such lesions outperforms MVFI, which – similarly to other non-contrast techniques – relies on flow-derived signal.

Our results demonstrate a marked advantage of MVFI over color-Doppler imaging, both in terms of spatial resolution, and ability to detect flow in small intralesional structures such as septa. This is in good agreement with several very recent studies where microvascular imaging has also been shown to have significant advantage in depicting septal flow within cystic renal lesions, and also within solid lesions of the kidney. We can conclude that in non-contrast US MVFI should be preferred over color-Doppler for investigating renal lesions, whenever available.

Study limitations: Most importantly this being a retrospective study the majority of lesions could not be included as either image documentation did not allow confident evaluation of lesion characteristics on MVFI, or the technique was not employed. This also raises the likelihood of selection bias, where “promising” lesions (larger, more complex, and/or better visualized) were more likely to be evaluated by novel techniques. Furthermore, retrospective evaluation was done using a non-blinded, expert consensus approach by the authors who have also performed the exams due to the limited number of expert users. From a technical standpoint MVFI setups were designed with non-contrast imaging in mind, thus the strong signal given by the contrast agent can actually deteriorate signal to noise ratio, and ring-down effects can occur behind larger vessels.

We conclude that using MVFI as an ancillary technique has a superior diagnostic yield than color-Doppler, and has a substantially higher chance to detect internal vascularity of renal lesions. However, its sensitivity is significantly lower for borderline (B2F in particular) lesions, thus it should not be used as a standalone tool at this point. Nonetheless, further investigations with prospective study design are clearly warranted.

The application of MVFI is becoming increasingly widespread, as sensitized Doppler techniques based on similar principles are available on almost all ultrasound systems from various manufacturers. Sensitivity varies depending on the manufacturer and model, but in general, these techniques allow for a more sensitive depiction of microvascularization compared to conventional Doppler methods. However, they share the same limitations, requiring careful attention to minimizing motion artifacts as much as possible. Additionally, the use of MVFI does not require special training, as there is currently less flexibility in adjustments compared to Doppler examinations.

Acknowledgements

First and foremost, I would like to express my heartfelt gratitude to my supervisor, Dr. Bálint Botz. Dr. Botz not only guided my work with his valuable suggestions and unwavering support but also shared his extensive knowledge in the fields of medical research and literature interpretation. Most importantly—and for this, I am profoundly grateful—he continuously encouraged me and never let me lose hope that it is possible to pursue research ambitions alongside clinical and teaching responsibilities. His immense contribution to our achievements cannot be overstated, and I cannot thank him enough for his dedication.

I am sincerely grateful to my colleague, Dr. Péter Farkas, who is among the most experienced radiologists in the field that forms the basis of my research, both nationally and internationally. I am especially thankful for his helpfulness and professional thoroughness, which were evident during our frequent consultations. Additionally, I deeply appreciate his willingness to integrate insights gained from daily clinical practice into the planning and execution of our research.

I am deeply grateful to Dr. István Battyáni, Prof. Péter Bogner, and Dr. Arnold Tóth, clinical directors of the Department of Medical Imaging at the University of Pécs, for their support throughout these years. They facilitated my research by providing the necessary instrumental background and assisting in the organization of the workflow. Within the framework of the opportunities at their disposal, they were always ready to help me.

Dr. Philip Manzoni, radiologist at the University Hospital of Besançon, has had a significant influence on my methodological approach, even without being aware of it. I had the privilege of working alongside him, and I would like to take this opportunity to express my gratitude for both his professionalism and his humanity.

Many thanks to Dr. Lars Thorelius, whose meticulous expertise, uncompromising professional approach, and freely shared knowledge profoundly shaped my mindset, even though he was likely unaware of the impact he had on me.

I am deeply grateful to Dr. Zoltán Harmat for introducing me to the application of CEUS techniques. I also owe many thanks to the assistants of the Department of Diagnostic Imaging, whose efficiency and flexibility made it possible to maintain a high standard of professionalism and a positive atmosphere even during a high volume of examinations. Finally, I would like to thank the physicians of the clinic for their valuable feedback, which greatly supported my work.

I am grateful to the other physicians of the clinic, including urologists, pathologists, and general surgeons, for generously sharing their knowledge with me and for their willingness to assist during consultations.

Although my friend Dr. Gábor Böhm works in a different scientific field, our conversations inspired me to explore new directions. I am grateful for this.

Finally, I would like to thank my parents, family, and friends for supporting and encouraging me through all these years.

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