Management of Indeterminate Cystic Kidney Lesions: Review of Contrast-enhanced Ultrasound as a Diagnostic Tool

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Indeterminate cystic kidney lesions found incidentally are an increasingly prevalent diagnostic challenge. Standard workup includes Bosniak classification with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). However, these tests are costly and not without risks. Contrast-enhanced ultrasound (CEUS) is a relatively new technique with lower risk of adverse events than iodine-containing contrast or gadolinium. In our review of the evidence for characterization of cystic kidney lesions with CEUS, CEUS displayed sensitivity (89%-100%) and negative predictive value (86%-100%) comparable to contrast-enhanced CT or MRI, with no decrease in specificity compared with CT and only a slight decrease compared with MRI. UROLOGY 87: 1–10, 2016. © 2015 Elsevier Inc.

Due to a rise in abdominal imaging, particularly among patients with chronic kidney disease and the elderly, physicians are detecting more kidney cysts and other indeterminate lesions in the kidney. The best approach to these cystic lesions, sometimes referred to as "incidentalomas," is not clear. The Bosniak classification system of kidney cysts, developed in 1986,[1] classifies lesions into categories (I, II, IIF, III, and IV) based on lesion size and density, number, thickness and enhancement of septa, calcifications, and nodularity. Categories I and II are generally considered benign; IIF requires follow-up; and III and IV are generally surgical lesions.

The recommendation for Class IIF and III lesions, which make up the greatest proportion of complex cystic lesions, is to perform repeat or follow-up contrasted imaging studies, which can often cause patient anxiety and add to the burden of healthcare costs. Biopsy is an alternative, but it poses risks to the patient and can often be nondiagnostic. The tests used to follow indeterminate lesions suffer from serious limitations in certain patient populations. For example, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) are contraindicated in patients with allergies to contrast agents, claustrophobia, or inability to lie flat or hold their breath. Most significantly, patients with moderate to severe renal insufficiency are both the highest risk group for developing complex lesions,[2] and have the highest risk of morbidity and mortality from CT or MRI contrast agents. An ideal diagnostic imaging modality would have fewer of these adverse features but remain highly sensitive and specific in differentiating malignant from benign disease.

More access to sensitive alternative imaging tools could improve management of indeterminate cystic kidney lesions and aid in the special at-risk populations. Current alternative imaging approaches include several highly nonsensitive modalities: B-mode ultrasound, Doppler ultrasound, and unenhanced CT and MRI. Contrast-enhanced ultrasound (CEUS) is also an emerging strategy that is being applied to these indeterminate cystic kidney lesions. CEUS of the kidneys, initially introduced in 1994,[3] utilizes a microbubble contrast agent that, unlike CT and MRI agents, is not filtered through the glomeruli but remains intravascular, making CEUS ideal for visualizing tissue vascularity without opacifying the urinary tract or surrounding parenchyma. The contrast agents SonoVue, Definity, and Optison are currently Food and Drug Administration approved only for cardiac use in the United States but approved for use in abdominal imaging outside the United States, in Europe, India, China, South Korea, and Brazil.

Whereas a recent review of new imaging modalities for indeterminate cystic kidney lesions included CEUS,[4] among other modalities, our review looks in depth at the evidence specifically related to CEUS, summarizing the current

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guidelines and diagnostic tools for characterizing cystic kidney lesions, reporting the existing evidence for application of CEUS to patients with indeterminate cystic kidney lesions, and comparing CEUS to conventional imaging modalities for cystic lesions to explore potential future clinical applications of CEUS in the kidney. To achieve this, we conducted a formal literature search with criteria shown in Supplemental Table S1. Our selection criteria were full-text, English language experimental studies in humans investigating CEUS for kidney lesions.

CURRENT CLINICAL GUIDELINES

Although international urologic and radiologic associations provide guidelines for management of indeterminate cystic kidney lesions, numerous differences across societies exist. The major urologic associations advise the use of contrast-enhanced CT as the primary test to characterize indeterminate cystic kidney lesions with contrast-enhanced MRI rated either equivalently or as a second option. The American College of Radiology rates contrast-enhanced CT the highest for those without kidney impairment whereas ratings for patients with kidney impairment are significantly different because of the nephrotoxic potential of contrast agents; subsequently, noncontrasted studies, though suboptimal, are relied upon (Supplemental Table S2).

The current role of ultrasound in clinical guidelines is variable. The American Urologic Association does not specifically address indeterminate cystic lesions; guidelines are therefore extrapolated from sections on asymptomatic hematuria and stage T1 incidentally detected renal masses. They indicate the need for alternative, low-risk imaging methods, including screening ultrasound. Similarly, the British Association of Urologic Surgeons/British Uro-oncology Group guidelines do not specifically address indeterminate cystic lesions, but in the guidelines for renal cancer, ultrasound is described as an initial screening modality. CEUS is mentioned only by the European Association of Urology, where SonoVue is approved for noncardiac applications and more widely utilized than in the United States.

BOSNIAK CLASSIFICATION OF CYSTIC KIDNEY LESIONS

The rate of malignancy of cystic kidney lesions correlates with Bosniak classification. The classification scheme initially sorted cystic kidney lesions into 4 categories based on lesion complexity and thus likelihood of malignancy. Category I and II lesions are generally considered benign with very minimal chance of malignancy. Radiographically, Bosniak I lesions have nonenhancing thin walls with no septa or solid components. Bosniak II lesions have minimally enhancing hairline thin septa with fine to slightly thickened calcifications. Class II lesions also include completely intrarenal, marginated, nonenhancing cystic masses less than 3 cm. Category IV lesions are nearly 100% malignant, warranting surgical removal in appropriate candidates. These lesions are cystic masses with enhancing soft tissue within the lesion and thickened, irregular, and enhancing walls or septa. Many category III lesions were initially removed surgically but found to be benign, prompting the development of category IIF—lesions worrisome enough to warrant follow-up but not worrisome enough to warrant surgery.[5] Management of these two categories, IIF and III, is the most challenging.

Category III lesions are generally accepted to be malignant 40%-60% of the time,[6,7] warranting surgical removal in the majority of cases.[7] These lesions have thickened, enhancing walls or septa with or without calcifications. Category IIF lesions have malignancy rates between 5% and 25%[6,8,9] and are generally followed with repeat imaging. These lesions are more complex than category II lesions with more septa and/or calcifications with minimal thickening and enhancement. This category also includes intrarenal, marginated, nonenhancing cystic masses larger than 3 cm. Recommended duration and frequency of follow-up is not clear and ranges from 1 to 5 years, depending on lesion complexity.[9,10] Repeated imaging with contrast-enhanced CT or MRI leads to high levels of radiation and/or contrast agent exposure, particularly an issue in younger patients. Therefore, ultrasound is sometimes used, although CT or MRI remains the most accurate test. A summary of the current management strategy, based on Bosniak classification, is provided in Figure 1A.

IMAGING/DIAGNOSTIC APPROACHES TO CYSTIC KIDNEY LESIONS

A summary of the standard diagnostic approaches to indeterminate cystic kidney lesions is provided in Supplemental Table S3. A brief description of the current role for each modality is provided below.

Conventional Ultrasound With Doppler

As many as 83%[11] of renal cell carcinomas (RCC) are revealed incidentally on conventional B-mode ultrasound. Conventional ultrasound is also an excellent test for simple cyst (Bosniak I and II) identification but lacks diagnostic accuracy for complex cysts (Bosniak IIF, III, and IV) as it provides no information on enhancement and small lesions <2 cm, which are difficult to visualize. Currently, unenhanced ultrasound is most commonly used in patients with chronic kidney disease when contrast-enhanced CT or MRI is contraindicated and as a follow-up imaging modality.

Contrast-enhanced CT

Contrast-enhanced CT is the most commonly used imaging test for characterization of indeterminate kidney lesions and is the test on which the Bosniak criteria were initially based. Although there has been some variability reported regarding the reliability of the CT-based Bosniak classification scheme,[12] CT remains the first study recommended by both radiologic and urologic associations (Supplemental Table S2).