Diagnostic performance of contrast-enhanced ultrasound in the evaluation of renal masses in patients with renal impairment

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ABSTRACT

Objective: To evaluate the performance of contrast-enhanced ultrasound (CEUS) in the risk stratification of indeterminate renal lesions picked up incidentally on abdominal imaging, in patients with renal impairment.

Methods: A retrospective study was performed of non-consecutive patients who underwent CEUS at our tertiary care centre for indeterminate renal lesions between March 2010 and September 2014. A total of 63 patients with 74 nodules were assessed with CEUS and stratified into either benign (Bosniak I, II, IIF) or suspicious for malignancy (Bosniak III, IV or hypervascular solid lesions). Diagnostic accuracy was determined by comparing these findings to subsequent histological diagnoses, temporal change after at least 20 months follow-up or after a diagnostic computer tomography / magnetic resonance imaging study.

Results: CEUS correctly identified 49/52 (94.2%) of benign lesions and 21/22 (95.5%) of malignant lesions, resulting in a sensitivity of 95.5% (95% CI 77.2-99.9%), specificity of 94.2% (95% CI 84.1-98.8%), positive predictive value (PPV) 87.5% (95% CI 67.6-97.3) and negative predictive value (NPV) 98.0% (95% CI 89.4-100%).

Conclusion: CEUS has high diagnostic performance in predicting the benignity of a renal lesion in patients with renal impairment, showing sensitivity and NPV approaching 100%.

KEY WORDS:
Contrast-enhanced ultrasound; renal cell carcinoma; indeterminate renal mass; complex renal cyst

INTRODUCTION

Renal lesions are common incidental findings in abdominal imaging, with cysts diagnosed in up to 35% of individuals after the 7th decade of life.[1] Although renal cell carcinomas (RCC) comprise a small subset, they are often initially detected on imaging, preceding any clinical signs.[2] Over 50% of RCCs are diagnosed first on imaging, and with its insidious growth, more than 60% of patients do not show any symptom of haematuria, abdominal mass or loin pain.[3,4] As such, RCCs have now become more a 'radiologist's tumour' with imaging raising the first suspicion. RCCs are often identified by their rich vasculature, an important finding that is only seen with contrast-enhanced imaging.[5-8] Although computer tomography (CT) and magnetic resonance imaging (MRI) remain the modalities of choice, the limitations imposed by renal impairment, contrast allergies, radiation and even technical and timing errors are disadvantageous.

In the last decade, contrast-enhanced ultrasound (CEUS) has begun making headway, as it is not subjected to the same limitations of CT and MRI, and is particularly useful in patients with renal impairment. After several consensus conferences since 2003, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) study group has developed guidelines and protocols for the use of CEUS, allowing a more standardised and reproducible practice of CEUS.[9]

Renal lesions are often better assessed on CEUS due to its greater sensitivity in depicting intracystic septations and cystic contents such as haemorrhage.[10] It also has high temporal resolution, that in combination with the lack of contrast excretion and background suppression of stationary tissue, has shown superior detection of microvascular flow within a lesion's septae and wall.[6,11,12] CEUS also has a larger margin for error, allowing repeated scanning in a single session.

Despite some conflicting data on RCC vascularisation patterns, published studies have generally been positive.[13] Of note, Barr et al evaluated the performance of CEUS in 1018 indeterminate renal lesions and showed high sensitivity 100%; specificity 95.0%; positive predictive value (PPV) 94.7%; and negative predictive value (NPV) 100%.[14] With advances in CEUS and the higher incidence of acute kidney injury (AKI) limiting the use of contrast-enhanced CT and MRI, CEUS may yet play a larger role in evaluating and differentiating benign from malignant renal lesions.[15] Our retrospective study aimed to evaluate the performance of contrast-enhanced ultrasound (CEUS) in the risk stratification of indeterminate renal lesions picked up incidentally on abdominal imaging, in patients with renal impairment.

This article was accepted: 25 July 2016
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MATERIALS AND METHODS

This study obtained ethical clearance from the National Healthcare Group Domain Specific Review Board (DSRB), and was granted exemption from obtaining informed consent as it was conducted in compliance with institutional policies, using a DSRB approved standard of care protocol. All imaging studies were reviewed on our institution's Radiology Information Service (RIS) and Picture Archiving and Communication System (PACS) database, while histological results were accessed through the Cluster Patients Records System (CPRS). No personal data was used and all data was anonymised without linkage to any personal information.

Patients

We retrospectively reviewed 63 non-consecutive patients from our tertiary care centre who underwent CEUS for indeterminate renal lesions between March 2010 and September 2014. The method used in detecting the incidental lesion(s) was not differentiated and came from all forms of abdominal imaging: gray-scale ultrasound, CT and MRI. The renal lesions were deemed indeterminate for several reasons, including those obtained from unenhanced studies or with inadequate phases, lesions affected by motion artefacts or those that were too small to characterize (TSTC). All patients had at least mild renal impairment at the time of CEUS study, in general agreement with our Departmental criteria of a Glomerular Filtration Rate (GFR) of less than 60 ml/min/1.73m^2. Cases in which there was a lack of histological diagnosis or insufficient follow-up period (arbitrarily taken as 20 months), or whereby there was poor visualisation of the entire lesion or the intracystic septae and/or peripheral wall due to thick calcification, were excluded from our study.

We included a total of 74 renal lesions for statistical analysis. The 63 patients consisted of 39 men (62%) and 24 women (38%), who had a mean age of 62.4 ± 14.5 years (range, 28 – 92 years). Seven of our patients underwent CEUS evaluation of 2 indeterminate renal lesions at the same sitting. One patient underwent CEUS follow-up 3 times, and 2 patients underwent CEUS follow-up 2 times of the respective same indeterminate renal lesion over the 4.5 year period of our study.

Imaging Techniques

All ultrasound studies were conducted by both a senior sonologist and a consultant radiologist with sufficient experience in CEUS. All studies were performed on either a Toshiba (Aplio 500, Toshiba Medical Systems Asia, Singapore) or Philips (iU22, Philips Healthcare, Singapore) ultrasound system with microbubble ultrasound contrast media (SonoVue, Bracco, Singapore). Each study began with a baseline unenhanced gray-scale ultrasound assessment, followed by CEUS with microbubble ultrasound contrast media (SonoVue, Bracco, Singapore), with 1.5 ml of Sonovue administered intravenously for each run.

Imaging Analysis

The gray-scale and CEUS images were collated, anonymised and read by a consultant radiologist who was blinded to the histological result and final outcome.

The malignancy criteria used for CEUS after microbubble injection was adapted from published enhancement patterns by Quaia *et al*, in turn borne out of previous literature.[5,16,17] We were in favour of these criteria, as we found the approach focused and practical, facilitating decision-making in patient management. Using this visual analysis, the reader was then asked to stratify the CEUS diagnostic confidence into two risk groups:

(1) Benign lesions were defined as those without solid components, showing enhancement of thin intracystic septae and/or enhancement of thin peripheral wall. These essentially include Bosniak I, II, IIF or non-enhancing lesions (Figure 1).
(2) Probably malignant lesions showing enhancement in thickened intracystic septae and/or enhancement in thickened peripheral wall and/or enhancing nodular elements. These lesions essentially include Bosniak III, IV or hypervascular solid lesions (Figure 2).

In addition to measuring the lesion's largest dimension, which has positive association with tumour progression, our study also calculated tumour volume (ml) using the prolate ellipse volume formula (height × length × width × π/6) which may be more important for prognostication in tumours less than 4 cm (i.e. pT1b).[18,19]

Reference Standard

Diagnostic accuracy was determined by comparing these CEUS findings to subsequent histological diagnoses. For lesions without histological correlation, the reference standard for benignity was either: (a) a minimum of 20 months stability in terms of size and morphology; (b) a reduction in the size of the lesion on follow-up; or (c) a conclusive CT or MRI study. The reference standard for malignancy was: (a) significant progression of the lesion in terms of size and complexity; or (b) evidence of metastases in the absence of another primary malignancy; both criteria being dependent on a consensus made in a multidisciplinary team setting. The arbitrary timeframe for follow-up was based on other published studies that have used interval stability between 12 and 36 months.[14,20-22]

This timeframe was felt adequate in detecting change as a previous meta-analysis, demonstrated that the mean growth rate of enhancing renal lesions was 0.28 cm a year (median 0.28 cm) and that RCCs show a mean growth rate of 0.40 cm a year (median 0.35 cm).[20,23] Watchful waiting for such lesions under 4 cm and a delayed surgical intervention also does not appear to significantly affect oncological outcome, nor increase surgical morbidity.[24,25] RCC can sometimes show very slow growth, but the risk of metastasis appear limited in these lesions.[26] The decision for follow-up and the choice of imaging modality used in follow-up studies was left to the preference of the referring clinician.

Statistical Analysis

Our results were analyzed using a computer software package (Analyze-It, version 1.63, Analyze-It Software, United Kingdom). The result of the CEUS studies was retrospectively considered a true-positive (if a malignant assessment matched a malignant reference standard), true-negative (if a benign assessment matched a benign reference

Table I: Numbers of benign and malignant renal lesions (X-axis) tabulated against lesions which were deemed benign or suspicious for malignancy on contrast-enhanced ultrasound (Y-axis)

	Benigh lesions	Malignant lesions	Total
Scan Malignant	3	21	24
Scan Benign	49	1	50

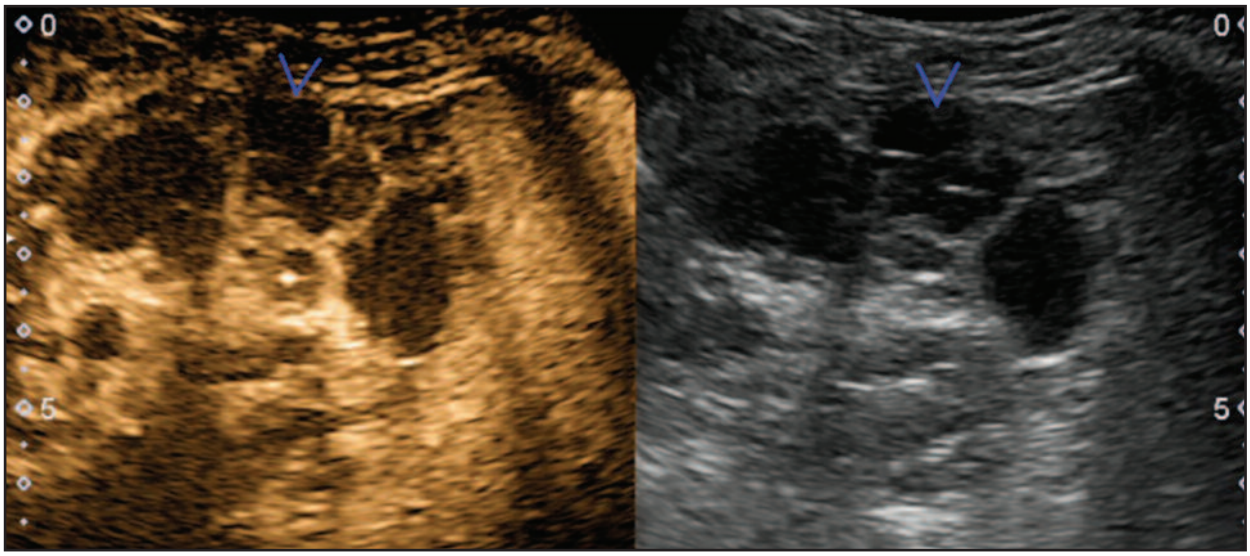

Fig. 1: Young female in her twenties with end-stage renal failure secondary to polycystic kidney disease. The lesion in question was a cyst in the interpolar region of the right kidney (blue arrow-heads), which showed enhancement of its thin peripheral wall and internal septa on contrast-enhanced ultrasound (left) but no suspicious enhancement characteristics, deemed a Bosniak 2 cyst. Histology revealed acquired cystic kidney disease with no evidence of malignancy.

standard), false-positive (if a malignant assessment matched a benign reference standard) or false-negative (if a benign assessment matched a malignant reference standard).

RESULTS

The 74 indeterminate nodules had a mean volume of 16.4 ± 33.4 ml (range 0.1 – 238 ml) with a mean maximum dimension of 2.8 ± 1.6 cm (range 0.4 – 7.9 cm) and underwent follow-up imaging for an average of 32 months. Of the 52 lesions that were benign; 5 were diagnosed histologically, comprising of 2 benign cysts, 1 lupus nephritis, 1 focal segmental glomerulosclerosis (FSGS) and 1 angiomyolipoma (AML); 2 were diagnosed with confirmatory contrast-enhanced CT, comprising of 1 AML and 1 Column of Bertin; 3 lesions became smaller or disappeared on follow-up imaging and the rest of the 42 lesions showed a minimum interval stability of at least 20 months (range 20 - 48 months).

Of the 22 malignant lesions; 12 showed significant progression on follow-up imaging while the other 10 were confirmed on histology (6 clear cell RCC, 3 papillary RCC and 1 lesion showed spindle and epithelioid cells where an angiomyolipoma could not be excluded).

Contrast-enhanced ultrasound correctly identified 49/52 (94.2%) of benign lesions and 21/22 (95.5%) of malignant lesions (Table I), resulting in a sensitivity of 95.5% (95% CI 77.2-99.9), specificity of 94.2% (95% CI 84.1-98.8%), PPV 87.5% (95% CI 67.6-97.3) and NPV 98.0% (95% CI 89.4-100%).

Amongst our three false positive cases, one showed macroscopic fat without calcification on CT that was in keeping with an AML and another was confirmed on histology as an AML (Figure 3). The only Bosniak category 3 cyst in our study became smaller after 14 months and was eventually considered benign, resulting in another false positive case (Figure 4).

Our study's only false negative case, was eventually diagnosed as a carcinoma on subsequent contrast-enhanced MRI and CT studies. A retrospective inspection of the CEUS study did not change our lesion classification, as again no enhancement was identified retrospectively. This may have been due to the medial location of the lesion and its small size (2 - 2.5 ml on both MRI and CT).

DISCUSSION

Renal lesions are common incidental findings on abdominal imaging, sometimes requiring further evaluation due to complex appearances such as thickened internal septations, calcification or increased density. Contrast-enhanced MRI and CT have routinely been the main modalities used for assessment, both of which show similar findings in most cystic renal masses.[27] Unfortunately, the administration of CT or MRI contrast is often precluded in patients with renal impairment, limiting these imaging modality options.

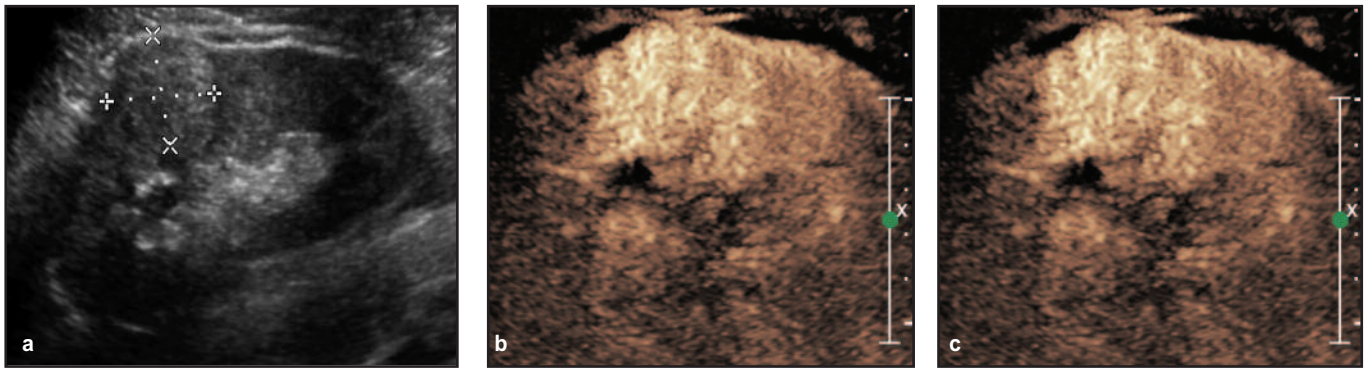

Fig. 2: Right renal lesion suspicious for malignancy on contrast-enhanced ultrasound, subsequently histologically proven to represent RCC.
(a) Longitudinal grey-scale ultrasound shows a heterogeneous, partially exophytic solid mass arising from the interpolar region of the right kidney.
(b) Post intravenous administration of 1.5 ml of Sonovue, the mass showed intense enhancement more than the surrounding renal parenchyma.
(c) There was evidence of washout within the lesion at about 1.5 minutes and more apparent at the 2 minutes mark post contrast administration.

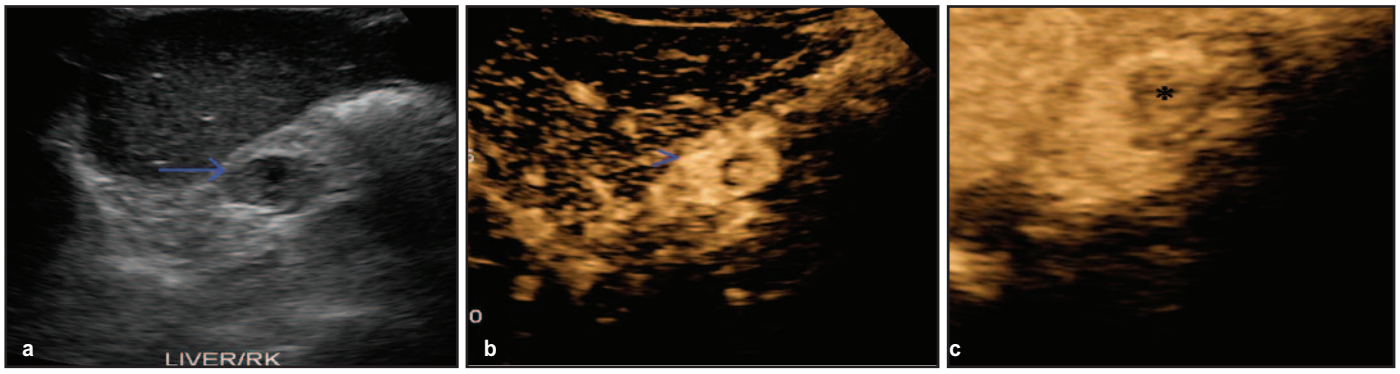

Fig. 3: One of our false positive cases, with contrast-enhanced ultrasound (CEUS) findings suspicious for malignancy but histology revealing AML.
(a) Longitudinal grey-scale ultrasound image shows the complex lesion in question in the interpolar region of the right kidney (blue arrow). Note the raised renal parenchymal echogenicity with poor cortico-medullary differentiation in this middle-aged male patient with end-stage renal failure.
(b) and (c) On CEUS, there was prompt hyper-enhancement immediately after contrast administration (blue arrow head), and washout beginning at 70 seconds post contrast administration (asterisk) which persisted on delayed scans.

Contrast use is important in identifying solid enhancing components, and the Bosniak classification generated from these studies are reproducible and have high accuracy in predicting malignancy.[28-30] This classification system can also be assessed by CEUS, with recent studies comparing CEUS and contrast-enhanced CT (CECT) showing no statistical difference between the two modalities in diagnosing renal malignancies.[17,32] Quaia *et al* asserted superior CEUS characterisation of complex renal cysts compared to CECT, with sensitivity of 81-95% (vs 86-95%), specificity of 42-68% (vs 63-79%), PPV of 61-74% (vs74-82%) and NPV of 67-89% (vs 83-92%) of CECT compared with CEUS across their three separate readers.[5] On a separate note, in a study comparing CEUS with MRI, Chen *et al* concluded that CEUS has higher diagnostic sensitivity and accuracy but lower specificity than MRI for classifying complex cystic renal masses (sensitivity 97.2% vs 80.6%, specificity 71.4% vs 77.1%, PPV 77.8% vs 78.4% and NPV 96.2% vs 79.4%).[33] Recently, a cohort of studies have published high sensitivity and negative predictive value of CEUS. Barr et al published sensitivity and negative predictive values of 100%, while Li *et al* reported sensitivity of 93.3% and negative predictive value of 99.2% respectively.[14,34] Our study results support these assertions, with a sensitivity of 95.5% and NPV of 98.0%.

A confounding factor in the interpretation of contrast-enhanced ultrasound studies has been the differentiation of malignancies from benign tumours and inflammatory lesions. This is due to the vascularity and enhancement of granulation tissue within these lesions that can mimic tumours. In our study, two of our false positive lesions were later diagnosed as AML on histology (Figure 3) or confirmatory CT. In one of the true positive lesions, we were also unable to completely exclude an atypical

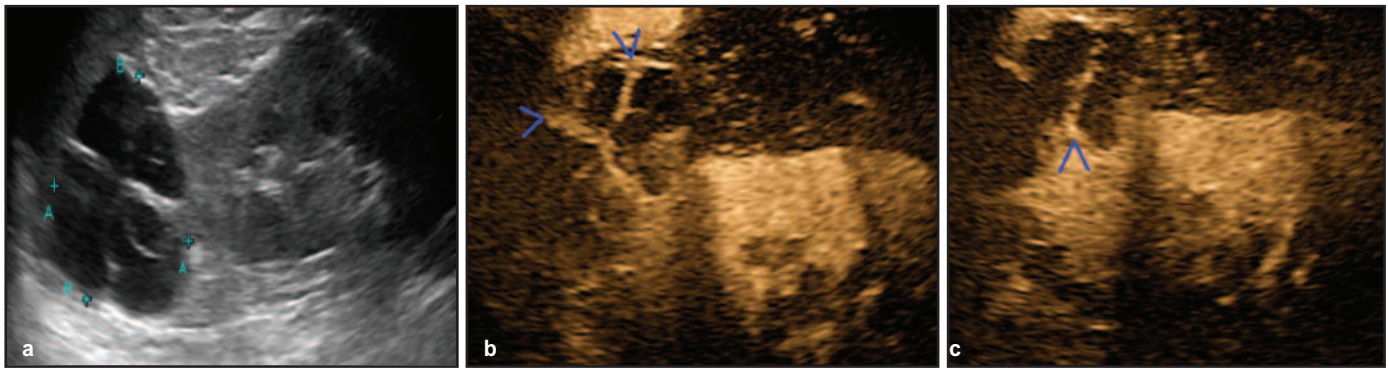

Fig. 4: Exophytic lesion arising from the left kidney upper pole deemed a Bosniak 3 cyst on contrast-enhanced ultrasound (CEUS). The patient had opted for expectant management, with the lesion demonstrating decrease in size on follow-up grey-scale US scan 14 months after this examination.
(a) Longitudinal grey-scale US image shows a multiseptated, exophytic cystic lesion arising from the upper pole of the left kidney.
(b) and (c) CEUS images show thickened and slightly nodular enhancing septae within the lesion (blue arrow-heads).

angiomyolipoma on histological evaluation. Our results are in line with other studies showing that approximately 30% of RCC mimic AML on ultrasound and that half of RCC can be hyperechoic.[35]

This study has several limitations. Firstly, this was a retrospective study with only qualitative assessment of enhancement patterns. This method is subject to inter-observer variations and was not addressed by our use of a single reader. Future prospective studies would certainly be beneficial in confirming our results. Secondly, there was a lack of histological diagnosis for a majority of benign lesions. Only five benign lesions were diagnosed histologically and it is impossible to guarantee that the remaining lesions would remain completely benign, noting that a few RCC can show very slow growth. Conversely, eleven malignant lesions also had no histological diagnosis and were based on worsening follow-up imaging. Because our study included older patients who already had renal impairment and often multiple other comorbidities, it was not uncommon for these patients to refuse further invasive tests, biopsies or treatment. Thirdly, our study categorised Bosniak category 2F cysts as benign and Bosniak category 3 cysts as malignant. Studies have proven cross-over of benign and malignant lesions in these two groups. Published data have shown that 10.9% of Bosniak category 2F lesions can progress to malignancy between 6 and 38 months.[36] Indeed, one of our false positive cases was a Bosniak category 3 cyst which became smaller after 14 months and was eventually considered benign (Figure 4).

CONCLUSION

In conclusion, CEUS has high diagnostic performance in predicting the benignity of a renal lesion in patients with renal impairment, with high sensitivity and negative predictive values approaching 100%.

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