

Is Contrast Enhanced Ultrasound a Valid Alternative Diagnostic Modality for Renal Cell Carcinoma in Patients with Renal Impairment?

Dear Editor,

With readily available cross-sectional imaging, small renal masses are increasingly being detected in asymptomatic individuals, prompting the need for further evaluation to exclude malignancy. Demonstration of contrast enhancement with a dedicated contrast-enhanced CT or MRI scan of the kidneys is the gold standard for radiologic diagnosis of renal cell carcinoma (RCC).¹ However, both CT and MRI contrast agents are contraindicated in patients with renal impairment.

Contrast-enhanced ultrasound (CEUS) employs the use of non-nephrotoxic, highly echogenic micro-bubbles that are able to enter the microcirculation and allow for dynamic, real time assessment of the arterial phase and vascular enhancement in RCC. While CEUS has been shown to be of use in diagnosis of renal lesions that are indeterminate on CT/MRI² in patients with normal renal function, it has not been evaluated in patients with renal impairment.

We aim to compare CEUS with current conventional imaging (CT or MRI) in the diagnosis of RCC.

Case Reports

Patient Selection

We selected all patients with histopathologically proven RCC, impaired renal function and preoperative CEUS identified from our institution electronic database (n = 10). Ethical approval was obtained from our Centralised Institutional Review Board (CIRB Ref: 2011/258/D).

Technical Details

CEUS was performed by trained specialist radiologists using 4.8 mL of intravenous Sulphur Hexafluoride micro-bubble ultrasound contrast agent (Sonovue) in 2 boluses. A Siemens ACUSON Sequoia™ 512 ultrasound system with contrast pulse sequencing capability was used. Each study involved active monitoring of the lesion of interest and surrounding areas in the early phase (range, 0s to 30s), late phase (range, 60s to 120s) and delayed phase (>120s). CEUS enhancement patterns, pseudo-capsule, neo-vessels, spoke-wheel and washout patterns were noted and recorded.

Analysis

CEUS films were reviewed by a CEUS-trained consultant radiologist blinded to the tissue diagnosis and CT/MRI

report. CEUS and conventional imaging outcomes (i.e. CT with or without contrast, MRI with or without contrast) of each patient were then classified into endpoints of 'RCC', 'Suspicious' or 'Inconclusive'. These endpoints were tabulated to assess agreement between CEUS and conventional imaging for diagnosis of RCC in these 10 patients.

Results

Our study included 7 males and 3 females. The mean age was 60.2 (± 9.4) years and the mean body mass index (BMI) 24.9 (± 4.1) kg/m². All the 10 patients had renal impairment with a mean GFR of 49.0 (± 27.7) mL/min. CT scan was performed in 8 of 10 patients (7 with contrast). MRI was performed in 4 of 10 patients (all with contrast). CEUS was performed in all 10 patients. All 10 patients had RCC at pathological examination of the surgical specimen.

CEUS correctly identified 7 lesions as RCC while conventional imaging correctly identified only 5 lesions (Table 1). No statistically significant difference was demonstrated between the sensitivities of the 2 tests (70% vs 50%). Furthermore, CEUS upgraded 2 of 4 lesions diagnosed as 'suspicious' by conventional imaging to 'RCC' and 1 lesion from 'inconclusive' to 'suspicious'.

Discussion

Radiological diagnosis of RCC is dependent on demonstration of lesional vascularity by contrast enhancement. However, CT contrast is known to cause contrast-induced nephropathy (CIN) in patients with renal impairment. The incidence of CIN is as high as 6.5% in

Table 1. Concordance between CEUS and Conventional Imaging

Diagnosis by Conventional Imaging	Diagnosis by CEUS			Total no. Diagnosed RCC by Conventional Imaging
	RCC	Suspicious	Inconclusive	
RCC	5	0	0	5
Suspicious	2	2	0	-
Inconclusive	0	1	0	-
Total no. Diagnosed RCC by CEUS	7	-	-	-

patients in CKD stages 3 to 5 (GFR <60 mL/min).³ At the same time, nephrogenic systemic fibrosis (NSF) is a problem with the use of Gadolinium-based contrast in MRI of patients with CKD stage 4 to 5 (GFR <30 mL/min). One hundred and forty-eight cases were reported with the use of Omniscan, a linear, non-ionic chelate of Gadolinium.⁴

As non-contrast CT and MRI have reduced confidence in diagnosis of RCC, patients with moderately severe chronic kidney disease often have to accept the risk of contrast-media exposure.

Rationale for use of CEUS in Diagnosis of RCC in Patients with Renal Impairment

CEUS allows dynamic, real-time visualisation of contrast enhancement, as well as the enhanced ability to detect blood flow. Contrast micro-bubbles (2 microns in diameter) rapidly enter even the smallest blood vessels in the lesion of interest alongside red blood cells (6 to 8 microns in diameter). CEUS has been shown to be superior in demonstrating lesional blood flow compared to power Doppler,⁵ as well as contrast CT.⁶ Compared to conventional Doppler ultrasound, CEUS demonstrates better visualisation of the RCC pseudo-capsule⁷ with good histologic correlation.⁸ Wink et al⁹ studied 20 renal masses in 18 patients, finding that out of 14 lesions identified as RCC on CEUS, 11 were confirmed on histology. The renal function of this group of patients was not reported.

In patients with renal impairment, CEUS micro-bubble contrast agents are not nephrotoxic and may be used with any level of renal function. In a European retrospective review of the use of SonoVue in more than 23,000 patients, Piscaglia and Bolondi¹⁰ reported only 2 serious adverse events with no deaths.

Our study is the first comparison between CEUS and conventional imaging in patients with renal impairment and we find that CEUS offers as good sensitivity in diagnosis of RCC (70%) as conventional imaging (50%).

Seven of the 8 CT scans and all 4 MRI scans were contrast-based in this study despite contrast not being recommended based on GFR levels. It remains speculative that the conventional imaging diagnosis of 'RCC' could have been less if non-contrast conventional imaging had been performed for the entire group.

CEUS is operator dependent and it may be limited in demonstrating tumour relationship to surgically important hilar structures. Therefore, CEUS does not replace conventional imaging procedure in patients without contra-indication for the use of contrast media. Rather, in patients with renal impairment, CEUS supplements the non-contrast cross-sectional study (CT/ MRI) by providing diagnostic information on lesional vascularity.

Conclusion

CEUS may be as sensitive as conventional imaging in detecting RCC in patients with a range of renal impairment. In this age of nephron-sparing surgery, CEUS as an alternative or adjunct to non-contrast conventional imaging in patients with renal impairment may improve confidence in RCC diagnosis while allowing nephrons to be spared even before surgery.

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