Contrast-enhanced ultrasonography (CEUS) for solid and complex cystic lesions assessment in renal transplant recipients (RTR) with acquired cystic kidney disease (ACKD): preliminary experience

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Purpose

Acquired Cystic Kidney Disease (ACKD) is defined as cyst formation in a non-cystic failed kidney and it is associated with the duration of dialysis. Its prevalence is 10-20% after 3 years, 50% after 5 years and rises up to 90% after 10 years of dialysis treatment.

ACKD is a well-known risk factor for renal cell carcinoma (RCC) which has been diagnosed in up to 19% of ACKD patients. Solid or cystic neoplasms can be identified (Fig.1).

The course of RCC appears to be more aggressive in renal transplant recipients (RTR) than in dialysis patients and it is therefore strongly advised to carry on close surveillance for RCC in RTR.

However, there is not a unanimous consent for surveillance modalities and timing and various strategies have been proposed (Fig.2).

US-based strategies in ACKD, although extremely safe, can be challenging in patients with high BMI or otherwise "difficult-to-image" kidneys; furthermore, US may not be accurate in the presence of small kidneys and deep/small lesions.

Currently, contrast-enhanced CT (CECT) is considered the main imaging modality for the detection of solid and cystic renal masses. However, it is frequently contraindicated in patients with mild to moderate renal insufficiency because of the risk of Contrast Induced Nephropathy (CIN). Even MRI, an efficient alternative modality, is burdened by the risk of nephrogenic systemic fibrosis.

In addiction these patients (RTR) have reduced compliance in performing radiological contrast examinations.

Second-generation US contrast agents consist of inert gas micro bubbles with stabilized shell in an aqueous suspension. They are purely intravascular, with a short lifetime (about 15 minutes) and are eliminated through the lungs, avoiding nephrotoxicity; therefore they can be safely administered to patients with renal failure.

Contrast-enhanced ultrasonography (CEUS) provides an easy and accurate depiction of microcirculation, not assessable by means of Doppler techniques. In kidneys it provides a detailed and clear view of renal vascularity with early enhancement in the arterial phase followed by a uniform enhancement of renal cortex and pyramids, until they become isoechoic with the cortex, in about 20-30 sec. CEUS has already been introduced in EFSUMB guidelines for the diagnosis of hepatic focal lesions.

In order to decrease the use of CECT and thus avoiding the risk of CIN in RTR with ACKD, we prospectively studied the usefulness of CEUS in characterizing complex cystic lesions and suspect solid masses.
**Fig. 0:** The Bosniak classification of renal cysts is considered an accurate and efficient method for treatment planning. This classification is based on CECT finding, but it could be applied also to MRI and CEUS.

1. All patients should have an ultrasound screening of their native kidneys once a year irrespective of ACKD.
2. Patients with ACKD and cysts according to Bosniak category I and II (benign simple cysts): Ultrasound screening twice a year; CT scan in the case of progressive lesions.
3. Patients with ACKD and cysts according to Bosniak category III (moderately complex cystic lesions): Ultrasound screening four times a year; CT or MRI scan once a year; nephrectomy in the case of progressive lesions, even if not reaching category III or IV.
4. Patients with ACKD and cysts according to Bosniak category III (‘indeterminate’ cystic masses) and IV (clearly malignant cystic masses): Nephrectomy.
5. Patients with ACKD in general: Generous indication for nephrectomy even in the lower categories, if progression occurs, because the original sense of the Bosniak classification (to preserve renal tissue by exact preoperative diagnosis) has lost its importance in patients with end-stage renal failure. This is true especially for cystic lesions of category III.

*ACKD, acquired cystic kidney disease; CT, computed tomography; MRI, magnetic resonance imaging.

**Fig. 0:** Recommendation for patient screening of the native kidneys in renal transplant patients according to the Bosniak renal cyst classification

Methods and Materials

From October 2009 to September 2010, 138 consecutive RTR underwent routine post-transplant US and in 43 (31%) ACKD was diagnosed. The patients with ACKD in which the US was considered suspicious or questionable were enrolled in this prospective study and underwent CEUS of their native kidneys. The study group comprised 23 patients (54% of those diagnosed with ACKD) with mean age of 58 years (range 44-69).

The patients with ACKD in which the US was considered suspicious or questionable were enrolled in this prospective study and underwent CEUS of their native kidneys.

CEUS was performed by a single experienced radiologist (more than 20 years in urologic ultrasound and more than 1 year in CEUS) with commercially available scanner (Esaote® MyLab 70 Gold) equipped with a software dedicated to the study with contrast, and with probe convex multi-frequency broadband 3-8 MHz. The lesions were scanned first by gray-scale US and color Doppler US to obtain their location and size and the best imaging plane from which both the lesions and the normal adjacent renal parenchyma could be observed. Thereafter, contrast enhanced agent (SonoVue, Bracco®, Milan, Italy) was injected intravenously as a bolus (average 2.5 ml/sec ) 4.8 ml dose followed by 10 ml of normal saline flush using a 18 or 20 G peripheral intravenous cannula. A low frame rate (5 Hz) and a very low mechanical index (MI=0.05-0.08) were used. Focus was always placed deeper than the nodule being examined. Each exam lasted about 3 min following bolus injection. One post-contrast cine clip was acquired lasting approximately 150 sec. If considered necessary, the injection was repeated 15 min later.

A quantitative analysis of enhancement was performed using a dedicated software for the quantification of perfusion QONTRAST (AMID Bracco®, Milan, Italy). This software elaborates color maps and process Time/Intensity (T/IS) curves on region of interest (ROI).

CECT studies (completed with Siemens AG, SOMATOM Sensation 16) were performed by experienced radiologists (average 10 years in urological CT imaging) blinded to the CEUS diagnosis (Fig.1).

In the interpretation of both CECT and CEUS findings, we used the Bosniak scheme for the classification of cystic lesions.

To date, we have carried out 11 controls at 6 months, and 4 at 9 months.
**Fig. 0:** Flow-chart

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Results

In the 23 patients studied by CEUS, 3 solid and 75 cystic lesions were identified (Fig.1). According to the Bosniak classification, 66 cysts were BI (Fig.2), 2 BII (Fig.3), 4 BIIF, 3 BIII. The 6 lesions classified BIII or solid were further studied by CECT scan.

CECT confirmed CEUS findings in 2 of the 3 solid lesions, both RCC at histology (Fig.4, 5) while the last one, diagnosed as an area of relatively spared parenchyma in atrophic kidney ("pseudo-tumor"), was simply monitored and did not change at follow up (Fig.6). In the 3 lesions classified as BIII by CEUS, CT confirmed 1 neoplasm (RCC at histology, Fig.7), while the other 2 were classified as BIIF, and remained unchanged at follow up (Fig.8). In BI, BII, BIIF cystic lesions no changes were observed at follow up (range of duration: 3-9 months).

In our initial experience, **CEUS has decreased by 78% the use of CECT (5/23).**

The use of CEUS was safe: no patient has suffered adverse reaction for CEUS; no renal function deterioration was noticed. The obvious limits of the study include the small number of cases and the short follow up.

CEUS allows the differentiation between hyperechoic cysts contents and solid masses, findings confirmed by CECT.

The quantitative assessments (T/IS curves) allows the differentiation between solid lesions and the surrounding atrophic parenchyma and the identification of pseudotumor, findings confirmed by CECT.

In difficult-to-image patients, CEUS permits the definition of cystic walls and septa characteristics.

CEUS allows the classification of complex cysts by ultrasound (in particular BIII cysts); findings partly confirmed by CECT, in part to confirm by follow up.

In BIII cysts we had CECT confirmation only in one case, resulted RCC, with derating to BIIF in two cases, unchanged until now. However, we can still assume the CEUS greater sensibility in the detection of enhancement (BIIF and BIII), according to literature.
Fig. 0: Results.

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Fig. 0: Example of BI cysts.
Fig. 0: Example of questionable cyst.

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Fig. 0: Patient 10 years after Renal Transplantation (RT). Solid lesion: variant of papillary renal adenocarcinoma, G3 Fuhrman.
**Fig. 0:** Patient 3 years after RT. Solid lesion: clear cell adenocarcinoma, G2 Fuhrman.

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**Fig. 0:** Patient 7 years after RT. Solid lesion: area of relative sparing parenchyma in atrophic kidney (pseudotumor).

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Fig. 0: Patient 8 years after RT. Cyst BIII: clear cell carcinoma, G1 Furhman.

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Fig. 0: Patient 3 years after RT. Cysts B III at CEUS, derating B IIF at CT.

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Conclusion

- CEUS is an extremely promising tool in the screening of native kidneys in patients affected by ACKD to rule out early RCC.

- The main advantage of this approach could be the ability to minimize the use of CECT thus avoiding the related risk of CIN, a goal particularly desirable in the setting of patients with impaired renal function such as RTR.

- In our experience, the method has proven to be safe, without significant side effects or adverse reactions, and appreciated by the patients. Further study and longer follow up will be needed to confirm our preliminary findings.
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