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Quantitative evaluation of contrast-enhanced ultrasound for differentiation of renal cell carcinoma subtypes and angiomyolipoma

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ABSTRACT

Purpose: To investigate the value of quantitative parameters of contrast-enhanced ultrasound (CEUS) in the differentiation of subtypes of renal cell carcinoma (RCC) and angiomyolipoma (AML).
Methods: The quantitative characteristics of 341 RCCs and 88 AMLs were analyzed with quantitative software (SonoLiver). Quantitative analysis was conducted in the whole tumor (ROI_{tumor}) and the maximum enhanced area of the tumor (ROI_{max}), acquiring the parameters of maximum intensity (IMAX), rise time (RT), time to peak (TTP), mean transit time (mTT), and area under the curve (AUC), were derived and analyzed. The difference values between ROI_{max} and normal renal cortex (ΔPar.s, including ΔIMAX, ΔRT, ΔTTP, ΔmTT, ΔAUC) were compared among renal histotypes.
Results: All time-related parameters (including RT, TTP and mTT) of ROI_{max} were shorter than the corresponding parameters of ROI_{tumor} in RCC subtypes (all $p<0.05$), but made no statistical difference in AMLs (all $p>0.05$). There were significant differences of all ΔPar.s among RCC subtypes and AML (all $p<0.01$). ΔIMAX and ΔAUC showed the trend that ccRCC > AML > pRCC = chRCC. ΔTTP showed AML = pRCC = chRCC > ccRCC, ΔRT and ΔmTT showed AML > pRCC = chRCC = ccRCC. ΔmTT could distinguish RCC from AML with the area under the ROC curve (AUC) of 0.86. The AUC of ΔIMAX and ΔAUC was 0.89 and 0.92 vs 0.85 and 0.85 for discriminating between pRCC (or chRCC) and AML vs ccRCC and AML.
Conclusions: Quantitative analysis of CEUS is a useful modality in AML and RCC subtypes' differentiation, by using ΔmTT, ΔIMAX and ΔAUC.

1. Introduction

As the most common benign and malignant solid lesions within the kidney, renal cell carcinoma (RCC) and angiomyolipoma (AML) are quite different from each other in clinical management and prognosis [1]. Most AMLs just need active surveillance instead of treatment unless it has clinical symptom or tumor size increases obviously, and angio-embolization represents its first-line active treatment [2]. But for RCC, surgical resection is the preferred therapy for local lesion. Patients with chromophobe renal cell carcinoma (chRCC) or papillary renal cell carcinoma (pRCC) have significant better prognosis than those with clear cell renal cell carcinoma (ccRCC). Moreover, whereas progressive treatment options, such as immunotherapy and targeted therapy, have been prompted by a better understanding of molecular biology, the response to these agents is influenced by the histological subtypes of RCC, as ccRCC is more sensitive to targeted therapy [3]. So a precise differential diagnosis of them is of paramount importance.

Contrast-enhanced ultrasound (CEUS), a safe and noninvasive imaging modality [4,5], has been demonstrated as a useful tool in the differential diagnosis of RCC and AML [6–8], such as heterogeneous peak enhancement, wash-out faster than renal cortex, and pseudocapsule sign are more common in RCCs and slow centripetal enhancement, homogeneous peak enhancement and slow wash-out in AML [6,9]. Among the RCC subtypes, hyper-enhancement at peak is more common in ccRCC than in pRCC and chRCC [6]. However, these CEUS features are subjectively qualitatively analyzed with low reproducibility.

Quantitative analysis of CEUS, based on software, is more objective and user-independent compared to qualitative analysis and has been demonstrated as a feasible and reproductive modality in differentiation of renal lesions [10–13]. However, it has been

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applied only in the differentiation of ccRCC and benign renal tumors or with small sample size. The difference of quantitative analysis among the main subtypes of RCC with a large series has been rarely investigated.

Thus, in the present study, we aimed to investigate the value of CEUS quantitative analysis in the differentiation of different RCC subtypes and AML.

2. Materials and methods

2.1. Patients

From February 2011 to February 2015, 757 consecutive patients, who turned to our hospital with undetermined renal tumors, underwent CEUS in our institution and their tumors were retrospective analyzed. Inclusion criteria were as follows: pathology proved by surgery or biopsy, no obvious movement of tumor in the video, enough solid component inside tumor and normal renal cortex adjacent to tumor. Exclusion criteria for quantitative analysis were as follows: pathological diagnosis was not acquired ($n = 154$), tumor with obvious movement in the video during the examination of CEUS due to either probe movement or respiration ($n = 60$), some rare tumors less than 10 ($n = 34$, 7 collecting duct carcinomas, 5 oncocytomas, 5 Xp11.2 translocation RCCs, 4 undifferentiated RCCs, 4 metanephric adenomas, 2 solitary fibrous tumors, 2 squamous-cell carcinomas, 3 congenital mesoblastic nephromas and 2 inverted papillomas), no renal cortex visible at the similar depth of tumor ($n = 20$), quality of fit (QOF) between the echo-power signal and the perfusion model lower than 80% during analysis ($n = 19$), the area of solid part in solid-cystic tumor smaller than 200 pixels (the lower limiting area of ROI in SonoLiver, $n = 59$). Therefore, 411 patients (267 male and 144 female, mean age, 54.12 ± 12.57 years, range, 20–83 years) with 429 pathologically proved renal masses were enrolled and retrospectively analyzed. The study was approved by the Ethical Committee of our institution (Zhongshan Hospital). The risks and benefits of CEUS were discussed with each patient and the informed consent was obtained before the CEUS was performed. Patients with serious cardiopulmonary disease, pregnancy, or lactation were excluded from this study.

2.2. Imaging technique

All the CEUS examinations were performed by one operator, experienced in abdominal ultrasonography and CEUS and was blinded to the diagnosis, with the E9 system (GE Healthcare, England; C1-5, 1–5 MHz). Initially, conventional ultrasound was performed to localize the renal mass in transverse and longitudinal sections, normal renal cortex adjacent to the mass was comprised and a single focus was set below the tumor, depth, overall gain, time gain compensation, and compression were optimized. Then, CEUS was performed at a mechanical index of 0.11 by using the second-generation contrast agent SonoVue® (Bracco, Italy). Contrast agent was injected into the ante-cubital vein as a bolus at a dose of 1.2 mL, followed by a flush of 5 mL of a 0.9% sodium chloride solution. Slow shallow breathing for patients was required when CEUS was conducted. The duration of CEUS was at least 3 min. The whole process of CEUS was recorded and saved on hard disk as DICOM-format.

2.3. Imaging analysis

The off-line quantitative analysis was performed with the software of SonoLiver (TomTec, Germany, and Bracco, Switzerland) by another sonologist who was blind to patients' other clinical

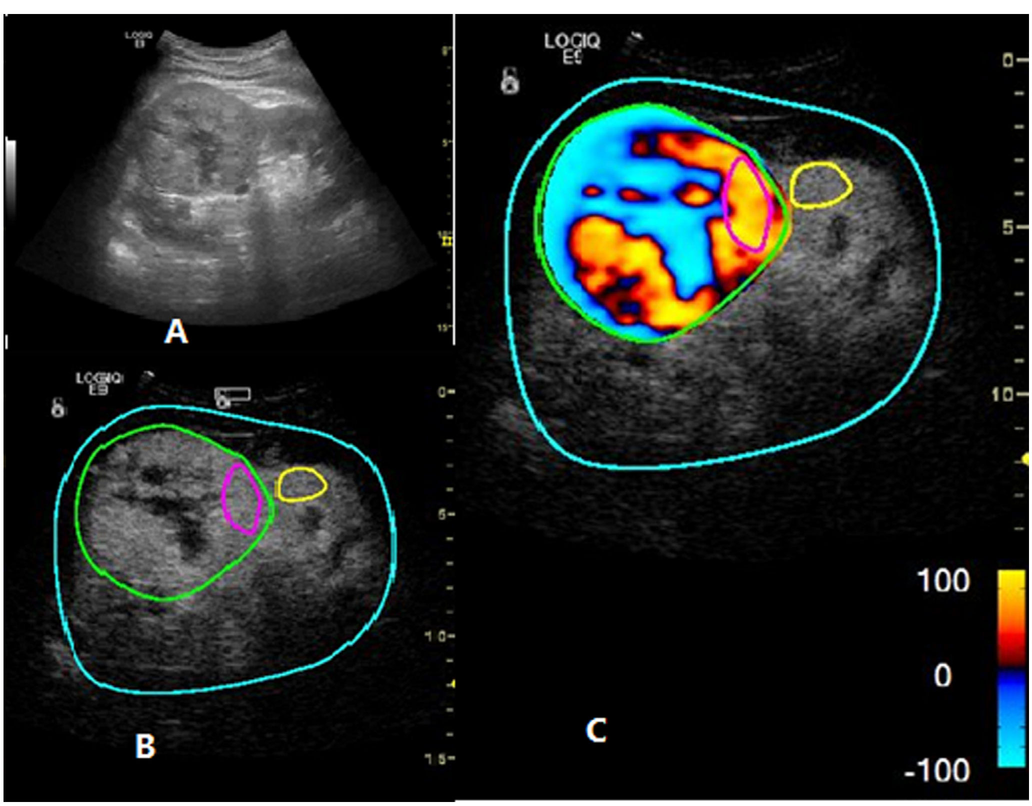

Fig. 1. The definitions of region of interest (ROI) A heterogeneously hyper-echoic lesion on baseline ultrasound (A), The lesion showed heterogeneously hyper-enhancement at peak on CEUS (B). The delimination ROI (turquoise) included the lesion and normal renal parenchyma, the ROI_{tumor} (green) outlined the whole lesion tissue and the ROI_{refer} (yellow) outlined the healthy normal renal cortex next to the lesion. ROI_{max} (magenta) was drawn based on the parametric color map (C) and it kept at the same depth as ROI_{refer}.