ORIGINAL ARTICLE

Comparing Sonazoid contrast-enhanced ultrasound to contrast-enhanced CT and MRI for differentially diagnosing renal lesions: a prospective multicenter study

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Abstract

Purpose To evaluate the diagnostic performance of contrast-enhanced (CE) ultrasound using Sonazoid (SNZ–CEUS) by comparing with contrast-enhanced computed tomography (CE–CT) and contrast-enhanced magnetic resonance imaging (CE–MRI) for differentiating benign and malignant renal masses.

Materials and methods 306 consecutive patients (from 7 centers) with renal masses (40 benign tumors, 266 malignant tumors) diagnosed by both SNZ–CEUS, CE–CT or CE–MRI were enrolled between September 2020 and February 2021. The examinations were performed within 7 days, but the sequence was not fixed. Histologic results were available for 301 of 306 (98.37%) lesions and 5 lesions were considered benign after at least 2 year follow-up without change in size and image characteristics. The diagnostic performances were evaluated by sensitivity, specificity, positive predictive value, negative predictive value, and compared by McNemar's test.

Results In the head-to-head comparison, SNZ–CEUS and CE–MRI had comparable sensitivity (95.60 vs. 94.51%, $P = 0.997$), specificity (65.22 vs. 73.91%, $P = 0.752$), positive predictive value (91.58 vs. 93.48%) and negative predictive value (78.95 vs. 77.27%); SNZ–CEUS and CE–CT showed similar sensitivity (97.31 vs. 96.24%, $P = 0.724$); however, SNZ–CEUS had relatively lower than specificity than CE–CT (59.09 vs. 68.18%, $P = 0.683$). For nodules > 4 cm, CE–MRI demonstrated higher specificity than SNZ–CEUS (90.91 vs. 72.73%, $P = 0.617$) without compromise the sensitivity.

Conclusions SNZ–CEUS, CE–CT, and CE–MRI demonstrate desirable and comparable sensitivity for the differentiation of renal mass. However, the specificity of all three imaging modalities is not satisfactory. SNZ–CEUS may be a suitable alternative modality for patients with renal dysfunction and those allergic to gadolinium or iodine-based agents.

Key Points

- This prospective multicenter study demonstrated that the diagnostic performance of SNZ–CEUS was comparable to CE–CT and CE–MRI.

- The three imaging modalities displayed desirable sensitivity, while the specificity needs to be further improved.
- CE–MRI may have better specificity than SNZ–CEUS for differentiating renal masses bigger than 4 cm

Abbreviations

ALMs	Angioleiomyomas
BMI	Body mass index
ccRCC	Clear-cell RCC
CE	Contrast-enhanced
CE–CT	Contrast-enhanced computed tomography

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CE–MRI	Contrast-enhanced magnetic resonance imaging
CEUS	Contrast-enhanced ultrasound
EAU	European Association of Urology
NPV	Negative predictive value
PPV	Positive predictive value
RCC	Renal cell carcinoma
SNZ–CEUS	Contrast-enhanced ultrasound using Sonazoid
TFE3	Transcription factor e3

Introduction

Renal cell carcinoma (RCC) was designated as being a top 10 cancer [1], which is one of the major public health problems [2]. The differentiation of malignant from benign renal lesions is essential for disease management and prognosis.

The latest 2020 European Association of Urology (EAU) guidelines specify that contrast-enhanced computed tomography (CE–CT) and contrast-enhanced magnetic resonance imaging (CE–MRI) are recommended for characterizing renal masses [3]. CT examination provides high definition and high spatial resolution. The application of MRI has been widened by the availability of advanced techniques such as diffusion-weighted and perfusion-weighted imaging [4]. However, CT examination requires the use of ionizing radiation along with potentially nephrotoxic contrast agents; and MRI examinations typically require extended image collection intervals and are not suitable for patients with metal implants or claustrophobia.

CEUS is easy accessibility and high reproducibility. Malignant renal masses show heterogeneous enhancement in cortical phase, and hypoenhancement to renal cortex in parenchymal phase according to previous study [5–7]. Sonazoid is a microbubble-based contrast agent consisting of perfluorobutane bubbles (mean diameter, 2.1 µm) that are stabilized using hydrogenated egg phosphatidylserine sodium [8]. Studies have shown that the lung is the major metabolic organ for the perfluorobutane component, avoiding possible nephrotoxicity [9]. Furthermore, this agent has strong, long-lasting contrast effects due to the low boiling point of perfluorobutane [10]. Therefore, it is preferred for patients with impaired kidney function or known allergic predispositions to contrast material containing iodine or gadolinium [11]. Thus, Sonazoid may provide a promising tool in the diagnosis of renal tumors.

Up to now, the diagnostic efficacy of contrast-enhanced ultrasound based on Sonazoid in renal tumors is still not clear. We carried out this multicenter study to evaluate the value of contrast-enhanced ultrasound with Sonazoid in differentiating benign and malignant renal tumors, and compared the differential diagnostic performance with CE–CT and CE–MRI.

Materials and methods

Patients

This prospective multicenter study was approved and supervised by the institutional review boards of seven participating institutions. The inclusion criteria were as follows: (1) age ≥ 18 years; (2) patient willingness to abide by the research protocol; (3) patients for whom SNZ–CEUS and CE–CT, or SNZ–CEUS and CE–MRI, were performed before the renal mass operation. The exclusion criteria were as follows: (1) unsatisfactory image; (2) undefined diagnosis (unclear histopathology diagnosis, or the follow-up period was less than 2 years for the renal mass without histopathology result); and (3) subjects who could not undergo CE–CT or CE–MRI. The SNZ–CEUS and CE–CT, or the SNZ–CEUS and CE–MRI, were performed within 7 days of one another, but the order of the examination sequence was not fixed.

SNZ–CEUS

For each center, all of the examinations were performed by a single operator with a minimum of 20 years of abdominal ultrasonographic expertise. A comprehensive evaluation of the renal mass was performed by two-dimensional ultrasound, including location, size, shape, echoic characteristics, etc., to define the optimal parameters for the examination by SNZ–CEUS. The mechanical index (MI) ranged from 0.18 to 0.20, thereby avoiding potential accidental damage from microbubbles. Following blending of Sonazoid with sterile physiological saline, a specified dose (0.015 mL/kg) of the solution was injected rapidly into the left elbow vein, immediately followed by a flush with 10 mL saline. Imaging features, including margin, shape, echogenicity, properties, enhancement model, pseudocapsule, homogeneity, unenhanced zone, wash-in and wash-out pattern were recorded. The enhancement model was classified as hyper-, iso-, and hypo-enhancement if the enhancement degree of lesion was higher, equal to or lower than the surrounding normal renal cortex. The wash-in and wash-out patterns of renal mass were defined as "early," "iso," or "later" compared to the peripheral renal parenchyma; The homogeneous or heterogeneous enhancement was defined as uniform distribution or with unenhanced areas in renal mass regardless of the enhancement degrees. The rim enhancement around the lesion and without washout on SNZ–CEUS is defined as pseudocapsule.

CE–CT and CE–MRI

Abdominal CE–CT scanning following intravenous administration of contrast agent was performed after the plain scan. Renal MRI examinations were performed on 1.5-T or 3-T MRI scanners. Non-contrast T1 images were acquired prior to administration of the agent. The sequences acquired by MRI include axial T1-weighted images, T2-weighted images, diffusion-weighted images, and contrast-enhanced MRI imaging.

Differentiation between benign and malignant lesions

The renal mass was classified as benign or malignant based on imaging examination. All characteristics were elucidated and reported at the ultrasonic examination by ultrasonologists with at least 20 years of abdominal imaging experience. The diagnostic result of the ultrasonic examination was acquired by radiologist with at least 20 years of abdominal imaging experience in each center, and the CEUS reports would be re-reviewed by another independent experienced ultrasonologists, and the discrepancy was solved by a more senior ultrasonologists. All of the CE–MRI and CE–CT imaging results were acquired from the original report, which was reviewed by a corresponding radiologist with at least 20 years of radiological expertise. As for the final imaging report, as long as the word "malignant" or "malignancy" was mentioned in the diagnostic result, the mass was regarded as malignant, including terms such as "considered malignant," "possibly malignant," "great possibility of malignancy," except for "not malignant". The diagnostic criteria for SNZ–CEUS are shown in Table S1. Lesions with hyper-, iso-, or hypo-enhancement in the cortical phase, and no washout in the parenchymal and late phase, or followed up for more than 2 years without any change (including size and image characteristics) were diagnosed as benign; heterogeneous echogenic masses with hyper-, iso-, or hypo-enhancement in the cortical phase that demonstrated washout in the parenchymal and late phase were considered malignant.

Statistics

Continuous variables are presented as mean ± standard deviation; categorical variables are presented as numbers and percentages. A non-paired Student's t test was performed for comparisons of normally distributed continuous variables. The diagnostic efficiency of different examinations was evaluated by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), as well as their 95% CI. Sensitivity was defined as the percentage of positive (malignant) confirmed by imaging and pathology at the same time to positive of pathology. Specificity was defined as the percentage of negative results (benign) confirmed by imaging and pathology at the same time to negative of pathology or stable in the follow-up period for more than 2 years. Variables with p values < 0.05 in univariate analysis were included in the multivariate analysis by logistic regression. Interobserver agreement for SNZ–CEUS feature was evaluated by Kappa or weighted Kappa test. The subgroup analyses were performed according to the size (1–4 cm, and > 4 cm). All statistical analyses were conducted as two-sided tests using SPSS 24.0; p values of < 0.05 were considered significant.

Results

Patients and tumor characteristics

323 patients were entered into this study between September 2020 and February 2021. Of these patients, 10 and 7 were excluded due to (respectively) unsatisfactory images and undefined diagnosis, Fig. 1. The diagnostic results were confirmed by histopathology (surgery resection:172/306, 56.21%, ultrasound-guided biopsy (129/306, 42.16%) or follow-up (5/306, 1.63%) for more than 2 years. 208 patients underwent both SNZ–CEUS and CE–CT scans, 114 patients underwent both SNZ–CEUS and CE–MRI examination, and 24 patients underwent all the three examinations. In 40 cases (40/306, 13.07%), the masses were benign lesions, including 25 angioleiomyomas (ALMs), 1 adenoma, 1 oncocytoma, 5 complex cysts, 3 instances of granulomatous inflammation, and 5 cases were followed up for more than 2 years without any size and image characteristics change. In 266 cases (266/306, 86.92%), the masses were diagnosed as malignant lesions, including 224 cases of clear-cell RCC (ccRCC), 7 cases of papillary RCC, 11 cases of chromophobe RCC, 14 urothelial carcinomas, and 10 other malignant carcinomas, including 1 Wilms tumor, 1 highly differentiated squamous cell carcinoma, 1 lymphoma, 3 metastatic tumors, 2 Xp11.2 translocation *TRANSCRIPTION FACTOR E3* (*TFE3*) gene fusion RCCs (Xp11.2/*TFE3* RCCs), 1 spindle cell carcinoma, and 1 fumarate hydratase (FH)-deficient RCC. The patients and tumor characteristics, classified based on benign and malignant lesions, are presented in Table 1.

Comparison of diagnostic efficiency between SNZ–CEUS and CE–CT

Of the 208 patients (208/306, 67.97%) examined by both SNZ–CEUS and CE–CT, 187 were concordantly and correctly diagnosed by both SNZ–CEUS and CE–CT, while 14 had divergent results. Of these 14 patients, 5 (4 with ccRCCs and 1 with complex renal cyst) were correctly diagnosed

Fig. 1 Flow chart for study enrollment. *CE–CT* contrast-enhanced computed tomography, *CE–MRI* contrast-enhanced magnetic resonance imaging, *CEUS* contrast-enhanced ultrasound
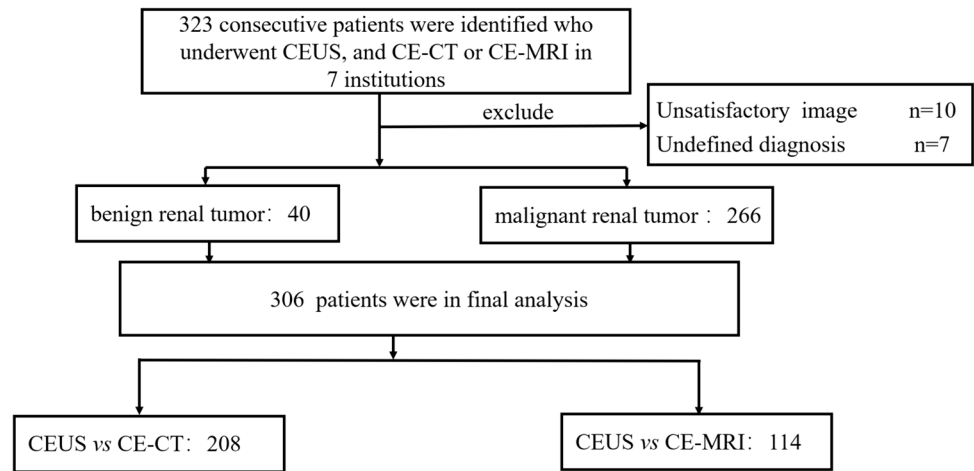

Table 1 Patients and tumor characteristics

Characteristics	Description	Benign ($n=40$)	Malignant ($n=266$)	p value
Age	Mean $\pm$ SD (years)	48.3 $\pm$ 15.9	55.2 $\pm$ 11.9	0.011
BMI	Kg/m^2	24.5 $\pm$ 4.16	25.0 $\pm$ 3.70	0.454
Diameter	Mean $\pm$ SD (cm)	5.30 $\pm$ 4.27	4.61 $\pm$ 2.33	0.325
Gender (%)	Female	30 (75.0)	94 (35.3)	< 0.001
	Male	10 (25.0)	172 (64.7)	
Margin (%)	Poorly definitive	14 (35.0)	123 (46.2)	0.245
	Well-definitive	26 (65.0)	143 (53.8)	
Shape (%)	Irregular	23 (57.5)	150 (56.4)	0.997
	Regular	17 (42.5)	116 (43.6)	
Echogenicity (%)	Hyper-echoic	11 (27.5)	71 (26.7)	0.073
	Hypo-echoic	15 (37.5)	62 (23.3)	
	Iso-echoic	6 (15.0)	30 (11.3)	
	Mix-echoic	8 (20.0)	103 (38.7)	
Property (%)	Cyst	2 (5.00)	4 (1.50)	0.136
	Cyst-solid	4 (10.0)	46 (17.3)	
	Solid	34 (85.0)	216 (81.2)	
Wash-out pattern (%)	Early	9 (22.5)	137 (51.5)	0.002
	Iso	20 (50.0)	72 (27.1)	
	Later	11 (27.5)	57 (21.4)	
Wash-in pattern (%)	Early	2 (5.00)	40 (15.0)	0.055
	Iso	26 (65.0)	181 (68.0)	
	Later	12 (30.0)	45 (16.9)	
Enhancement model (%)	Hyper	9 (22.5)	187 (70.3)	< 0.001
	Iso	12 (30.0)	44 (16.5)	
	Hypo	19 (47.5)	35 (13.2)	
Homogeneity (%)	Heterogeneous	12 (30.0)	151 (56.8)	0.003
	Homogeneous	28 (70.0)	115 (43.2)	
Unenhanced zone (%)	No	30 (75.0)	107 (40.2)	< 0.001
	Yes	10 (25.0)	159 (59.8)	
Pseudocapsule (%)	No	32 (80.0)	222 (83.5)	0.751
	Yes	8 (20.0)	44 (16.5)	

Qualitative variables are expressed as n (%), and quantitative variables are expressed as Mean $\pm$ SD

by SNZ–CEUS but misdiagnosed by CE–CT. Among the 4 cases of ccRCC, 2 were misdiagnosed as adenomas and 2 as ALMs; the complex renal cysts were misdiagnosed as RCC. 1 oncocytoma was misdiagnosed by both SNZ–CEUS and CE–CT. In the head-to-head comparison between SNZ–CEUS and CE–CT (Table 2), the sensitivity (97.31 vs. 96.24%, $P = 0.724$), the specificity (59.09 vs. 68.18%, $P = 0.683$), positive predictive value (95.26 vs. 96.24%) and negative predictive value (72.22 vs. 68.18%) were similar between them. There was no statistical difference for sensitivity and specificity between the two examinations in terms of nodules bigger than 4 cm (Table S3).

Comparison of diagnostic performance between SNZ–CEUS and CE–MRI

SNZ–CEUS and CE–MRI showed comparable sensitivity (95.60 vs. 94.51%), positive predictive value (91.58 vs. 93.48%) and negative predictive value (78.95 vs. 77.27%) in the head-to-head comparison, the specificity of CE–MRI was more desirable than SNZ–CEUS (73.91 vs. 65.22%, $P = 0.752$) (Table 2). The CE–MRI has higher specificity than SNZ–CEUS (90.91%, 95% CI 58.72–99.77 for CE–MRI vs. 72.73%, 95% CI 39.03–93.98 for CEUS) for nodules > 4 cm when didn't compromise the sensitivity (Table S4). Among the 114 patients (114/306, 37.25%) that underwent both SNZ–CEUS and CE–MRI examinations, 4 patients with ALM were incorrectly classified by SNZ–CEUS but correctly diagnosed by CE–MRI. Four patients with ccRCC were correctly classified by SNZ–CEUS but incorrectly diagnosed by CE–MRI. Another 3 patients were misdiagnosed by both SNZ–CEUS and CE–MRI, including, 1 adenoma and 1 case with complex renal cysts that were misdiagnosed as malignant; and 1 ccRCC that was misdiagnosed as benign.

Discussion

The study evaluated the diagnostic efficacy of Sonazoid-based contrast-enhanced ultrasound in renal tumors, and compared it with CT and MRI. The SNZ–CEUS showed satisfactory diagnostic efficiency in differentiating benign and malignant renal tumors, which provided a basis for its application in the diagnosis of renal tumors.

The diagnostic applications of CEUS in the characterization of renal masses have been investigated extensively. Previous research revealed that CEUS has high sensitivity (ranging from 93 to 97%), which is consistent with the result in this study (ranging from 95.60 to 97.31%) [12, 13]. The specificity of CEUS is lower than that of CE–CT (59.09 vs. 68.18%, $P = 0.683$) and CE–MRI (65.22 vs. 73.91%, $P = 0.752$), and the specificity all of three examination is lower than that of sensitivity. Among the benign tumors, more than half (25/40, 62.5%) were ALM and the rest of them incorporated various tumor types with atypical features. Therefore, it was hardly to find a uniform pattern of enhancement, which made the determination of benign tumors difficult, consequently may interpret the low specificity.

Comparative diagnosis between ALM and ccRCCs were the focus of this study. The image characteristics of two tumor types often overlap, which may impede effective diagnosis between them. In the head-to-head comparison, 4 patients with ccRCCs were misdiagnosed by CE–CT and CE–MRI, respectively, and 4 ALMs were incorrectly classified by SNZ–CEUS. A previous study reported that the percentage of macroscopic fat is a key criterion for diagnosing ALM [5], and ALMs typically contain macroscopic fat. Early studies also reported difficulties in discriminating between ALM and RCC [14]. A prospective study by Ascenti et al. [15] showed that ALM had a large range of variable characteristics concerning contrast enhancement. Smaller ccRCCs also have been reported to demonstrate homogeneous enhancement [16], and some ALM cases can present as hyperenhancement and pseudocapsules or more complicated image representation [17] on CEUS images.

Table 2 Diagnostic performance of CEUS and CE–MRI, CEUS and CE–CT in the head to head comparison

	208 Nodules in 208 patients			114 nodules in 114 patients		
	SNZ–CEUS	CE–CT	P^a value	SNZ–CEUS	CE–MRI	P^a value
Se (95% CI) (%)	97.31 (93.84–99.12)	96.24 (92.4–98.47)	0.724	95.60 (89.13–98.79)	94.51 (87.64–98.19)	0.997
Sp (95% CI) (%)	59.09 (36.35–79.29)	68.18 (45.13–86.14)	0.683	65.22 (42.73–83.62)	73.91 (51.59–89.77)	0.752
PP V (95% CI) (%)	95.26 (88.83–98.43)	96.24 (90.75–98.47)		91.58 (81.23–97.61)	93.48 (84.36–97.84)	
NP V (95% CI) (%)	72.22 (52.24–87.33)	68.18 (50.47–86.14)		78.95 (58.56–91.08)	77.27 (58.37–91.33)	

Se sensitivity, *Sp* specificity, *PPV* positive predictive value, *NPV* negative predictive value

[a]*p* value was acquired by McNemar's test

Resolution of temporal and space-related properties is much higher with CEUS than that with CT or MRI [18]. Consistent with that interpretation, an early study suggested CEUS as an alternative to MRI for imaging examination and diagnosis of renal masses [19, 20]. Previous work has shown that the majority of malignant renal masses show heterogeneous enhancement, given that invasive growth was more likely to lead to bleeding; thus, malignant renal masses often contain hemorrhages or necrotic regions, such that imaging with CE agents exhibits nonenhanced areas. In this study, unenhanced zone within the tumor was the independent risk factor between benign and malignant renal mass.

This study has some limitations. First, CEUS was performed by 7 radiologists from 7 centers, the report may be affected due to the highly operator-dependent property of CEUS, although each operator with a minimum of 20 years of abdominal ultrasonographic expertise. Second, there is no strict criterion for the choice of CE–CT or CE–MRI, about half of the renal masses (129/306, 42.16%) were cured by ultrasound-guided microwave ablation, and the study incorporate 5 lesions without histopathological confirmation, all the factors may lead to potential selection bias. In addition, the scanners and contrast agents used for CT and MRI at different institutions may slightly discrepant, which might affect the diagnostic performance.

Conclusions

This study confirmed that SNZ–CEUS is a valuable diagnostic tool for differentiating renal masses. Given the known limitations of CE–CT, which may expose to the ionizing radiation, and CE–MRI, which cannot be used in patients with metal implants or claustrophobia, SNZ–CEUS may be a suitable alternative modality for patients with renal dysfunction and those allergic to gadolinium or iodine-based agents.

Declarations

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