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ARTICLE

Single-center study: the diagnostic performance of contrast-enhanced ultrasound (CEUS) for assessing renal oncocytoma

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ABSTRACT

Purpose: The aim of the present retrospective single-center study is to evaluate the diagnostic performance of contrast-enhanced ultrasound (CEUS) in the evaluation of renal oncocytoma.

Method: Thirteen patients with histopathologically confirmed renal oncocytoma and 26 patients with histopathologically confirmed renal cell carcinoma were included in this retrospective single-center study on whom CEUS was performed between 2005 and 2015. The applied contrast agent was a second-generation blood pool agent. CEUS examinations were performed and interpreted by a single radiologist with more than 15 years of experience (EFSUMB Level 3).

Results: CEUS examinations were successfully performed in all included patients without any adverse effects. Renal oncocytomas showed varying echogenicity (46% hypoechoic, 23% hyperechoic, 8% iso-/hyperechoic, 8% isoechoic). In two cases renal oncocytoma only demarcated upon i.v. application of contrast medium. In bilateral oncocytosis, lesions presented as hyperechoic. Only 23% of renal oncocytomas showed slight vascularization using Color Doppler. No oncocytoma-specific pattern of microperfusion could be elucidated: 85% of the oncocytomas presented hyperenhancing, of whom 50% also showed delayed venous wash-out; 8% of renal oncocytomas showed venous wash-out without early arterial hyperenhancement.

Conclusions: Within the frame of the present study and in line with the recent state of knowledge, no specific sonomorphological feature – including CEUS – could be detected allowing for adequate discrimination between oncocytoma and renal cell carcinoma.

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Introduction

Renal oncocytoma depicts a predominantly benign epithelial tumor of the kidney which still remains challenging to histopathologically diagnose [1]. It is comprised of epithelial cells with an eosinophilic granular cytoplasm due to its large amount of mitochondria.

Oncocytomas account for 4–7% of all renal neoplasms [2,3] and typically present solitarily in patients between the 5th and 8th decade [4], with a male predominance (1.7:1). The tumor diameter may vary up to 26 cm [4]. In rare cases the metastasis and infiltrative growth of oncocytomas were described [3], thus its benign nature has still been a matter of debate [5].

Certain oncocytoma-associated chromosomal alterations, like loss of chromosome 1 [6], chromosomal translocations, especially involving chromosome 11 [7] or impairment of mitochondrial DNA [8], were described.

Moreover, bilateral and multiple renal oncocytomas are associated with hereditary syndromes like Birt-Hogg-Dubé syndrome and tuberous sclerosis [1,9]. The majority of patients stay clinically asymptomatic, thus in most cases oncocytomas are incidentally found. Massive tumor growth may result in an abdominal palpable mass. Moreover, some patients may present with flank pain, hematuria, arterial hypertension, weight loss or fever. Oncocytic lesions can be difficult to be histopathologically scrutinized from renal mass biopsy (RMB), as a recent meta-analysis of 205 oncocytic renal tumors elucidated a positive predictive value of 67% of oncocytoma on RMB with a distinct heterogeneity between included studies [10,11]. Due to the difficult non-invasive diagnosis of oncocytomas, most patients undergo surgical resection which allows for histopathological validation of the diagnosis. Recently, four microRNAs were reported as specific urinary biomarkers for oncocytomas [12].

The sonographic features of renal oncocytomas described in a study in 1984, as diameter <5.5 cm, well-circumscribed, homogenous and isoechogenic to renal parenchyma, were proven to be unreliable since some renal cell carcinomas (RCC) may similarly appear [13]. Moreover, the often oncocytoma-related central scar could only be seen in one out of four cases [14].

Still, to date, oncocytomas cannot be sufficiently differentiated from renal cell carcinoma by CT or MRI imaging [15,16].

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Table 1. Sonomorphological features of renal oncocytomas.

Patient	Location	Size (cm)	Echogenicity (native B-mode)	Vascularization (Doppler mode)	Contrast CEUS
#1	Left	2.3	Hypoechoic	–	+
#2	Left	1.0	—	–	+ / wo
#3	Left	0.6	Hyperechoic	(+)	+ / wo
#4	Right	2.0	Hypoechoic	–	+ / wo
#5	Right	1.5	Hypoechoic	–	+
#6	Left	2.0	Hyperechoic	–	+
#7	Left	1.7	—	–	+
#8	Bilateral	<1.0 cm	Hyperechoic	–	–
#9	Right	2.7	Iso-/hyperechoic	–	+ / wo
#10	Left	1.5	Isoechoic	–	wo
#11	Right	3.6	Hypoechoic	(+)	+ / wo
#12	Right	2.0	Hypoechoic	(+)	+
#13	Left	5.0	Hypoechoic	–	+

wo, wash-out; (+), slight vascularization in Doppler mode; +, contrast enhancement in CEUS; −, negative.

Likewise, for CT and MRI imaging, in the sparse studies assessing the diagnostic performance of CEUS for oncocytoma evaluation, no reliable features could be described distinguishing oncocytoma from RCC [17–19].

The aim of the present single-center study was to evaluate the diagnostic performance of CEUS in assessing oncocytoma patients.

Materials and methods

This retrospective single-center study was approved by the local institutional ethical committee of the institutional review board and all contributing authors followed the ethical guidelines for publication in *Scandinavian Journal of Urology*. All study data were gathered according to the principles expressed in the Declaration of Helsinki/Edinburgh 2002. Oral and written informed consent of all patients were given before CEUS examination and their associated risks and potential complications have been carefully described. All CEUS examinations were performed and analyzed by a single skilled radiologist with more than 15 years of clinical experience (EFSUMB Level 3). All included patients underwent native B-mode, Color Doppler and CEUS scans. Up-to-date high-end ultrasound systems with adequate CEUS protocols were utilized (GE Healthcare: LOGIQ E9; Samsung RS80A Prestige, Siemens Ultrasound Sequoia S20000, S3000, Philips Ultrasound iU22, EPIQ 7). A low mechanical index was used to avoid early destruction of microbubbles (<0.2). For all CEUS examinations, the second-generation blood pool contrast agent *SonoVue*® (Bracco, Milan, Italy) was used [20–24]; 1.0 − 2.4 mL of *SonoVue*® was applied. After contrast agent was applied, a bolus of 5 − 10 mL sterile 0.9% sodium chloride solution was given. No adverse side-effects upon administration of *SonoVue*® were registered. All CEUS examinations were successfully performed and the image quality was sufficient in every single case, allowing for proper analysis of the sonomorphological appearance of the renal lesions. The patient files and imaging records were retrieved from the picture archiving and communication system (PACS) of our institution.

The vascular phases of CEUS were defined as the cortical phase (8–35 s after i.v. injection), corticomedullary phase (36–120 s after i.v. injection) and late phase (>120 s to the disappearance of the microbubbles). Dynamic contrast differences in the perfusion of the renal parenchyma compared to the lesions were evaluated with qualitative analysis of wash-in and wash-out characteristics. Evaluation of morphological features included: location, size and shape of the lesion; the echogenicity of the tumors which could be hypoechoic, isoechoic or hyperechoic or non-visible in native B-mode. Vascularization was evaluated using Color Doppler and CEUS. Retrospective analysis of archived cine-loops of all included patients was performed.

A total of 13 patients with histopathologically confirmed renal oncocytoma on whom CEUS was performed between 2005 and 2015 were included in the study. The mean age of the patients at the time of CEUS performance was 70 years (min = 53; max = 79). There were eight men and five women included in this study (ratio 1.6:1).

Twenty-six patients with histopathologically validated renal cell carcinoma were included in the control group: nine patients with clear cell renal carcinoma (CCRCC), 10 patients with papillary renal cell carcinoma (PRCC) and seven patients with chromophobe renal cell carcinoma (ChRCC). The mean age of the patients of the control group at the time of CEUS examination was 63 years (min = 32; max = 84). Eighteen male and eight female patients were included in the control group (ratio 2.2:1).

All patients with solitary renal oncocytoma underwent partial nephrectomy, patients with renal cell carcinoma underwent either partial or radical nephrectomy in the local Department of Urology. The histopathological analysis was performed in collaboration with the local Institute of Pathology.

Results

CEUS examinations were performed on all 13 included patients without occurrence of any adverse effects. Twelve unilateral lesions and one case of bilateral oncocytosis were analyzed. In seven cases oncocytomas were located in the left kidney, in five cases they were located within the right kidney. The average diameter of the unilateral lesions was 2.0 cm (min = 0.6 cm; max = 5.0 cm). In the included case of bilateral oncocytosis, multiple renal lesions measuring

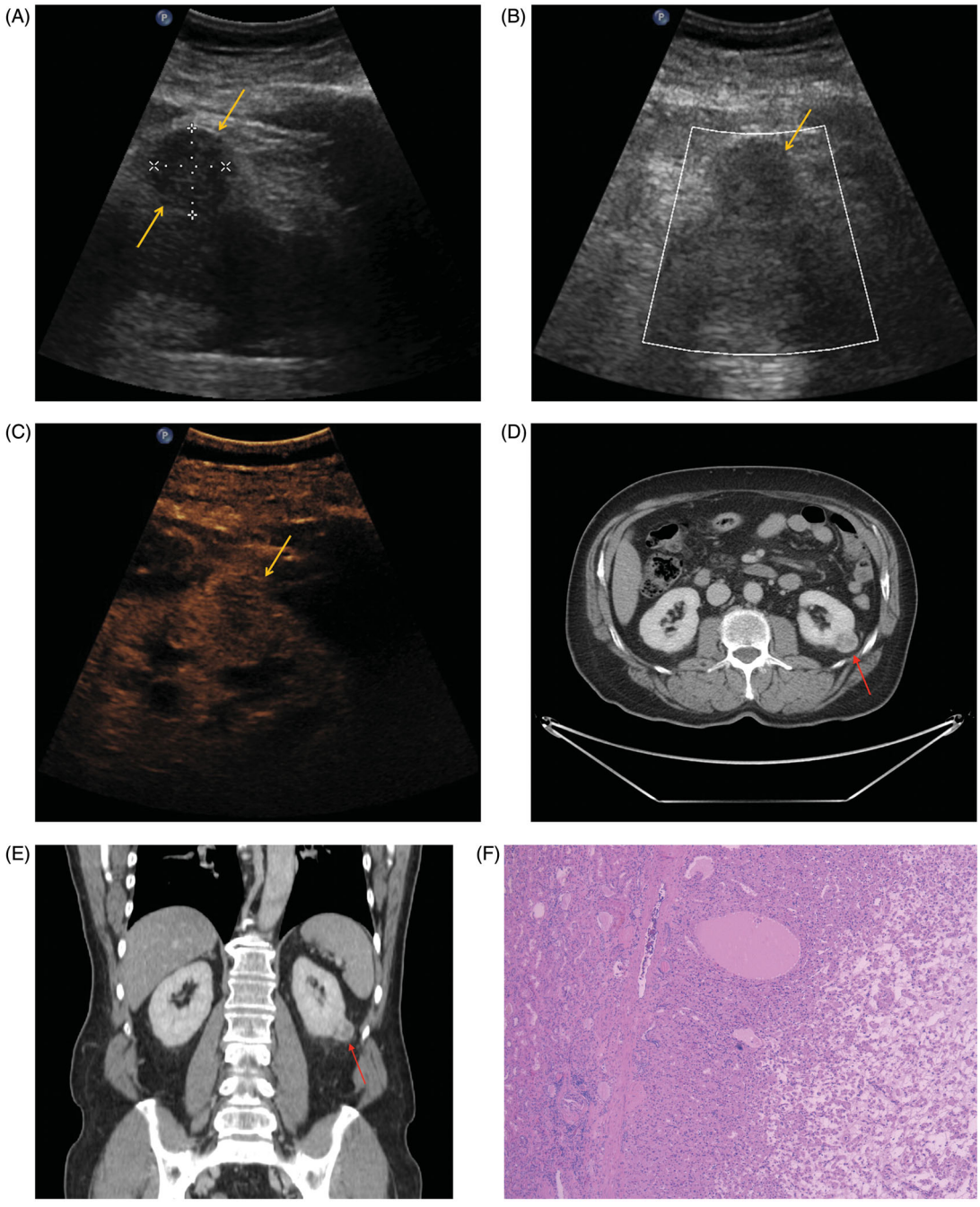

Figure 1. Unilateral renal oncocytoma in the left kidney. In patient #1 a hypoechoic lesion in the middle third of the left kidney with a diameter of 2.3 cm (yellow arrows) in native B-mode (A) and without vascularization in Doppler mode (B) could be registered. Upon application of *SonoVue*®, rapid contrast enhancement of the lesion could be detected (C, yellow arrow). Corresponding contrast-enhanced CT scan reveals partially and inhomogeneously enhancing renal lesion (red arrows), venous phase in axial (D) and coronal (E) reformation. Hematoxylin and eosin staining of the resected renal oncocytoma showing large cells with eosinophilic granular cytoplasm ('oncocytes') in the right (F).

<0.1 cm were observed. The ratios of left-to-right tumor location for the control group were: CCRCC = 4:5, PRCC = 3:7 and ChRCC = 2:5.

The echogenicity of the lesions depicted to be heterogenous (Table 1). In six cases (46%) lesions presented as hypoechoic in native B-mode, compared to three cases (23%) of hyperechoic lesions, one (8%) iso-/hyperechoic lesion and one (8%) isoechoic lesion; in patients #2 and #7, renal lesions only demarcated upon application of contrast medium and no morphological correlate in native B-mode or Doppler mode could be detected.

In only three (23%) cases slight vascularization of the lesion could be detected by using Color Doppler. In 11/13 (85%) patients a rapid uptake of *SonoVue*® could be registered (Figure 1); five of those 11 contrast-enhancing lesions also showed venous wash-out (Figure 2). Patient #8 showed multiple bilateral small hyperechoic lesions with a similar uptake of contrast medium like the surrounding renal parenchyma; underlying oncocytosis was histopathologically confirmed. In patient #10 (8%), besides no uptake of contrast medium being seen, delayed venous wash-out was registered (Figure 2).

In Table 2 the varying sonomorphological features of the three most frequent different histologic sub-types of RCC of the control group are illustrated. The malignant renal cell carcinoma lesions also showed heterogeneous echogenicity. For the CCRCC sub-type, 3/9 lesions were hypoechoic (33%), 1/9 was hyperechoic (11%) and 4/9 lesions were isoechoic (44%). In one case (patient #2), the CCRCC lesion only demarcated by applying Color Doppler and upon intravenous administration of contrast medium. The PRCC lesions were in 6/10 cases hypoechoic (60%), hyperechoic in 3/10 cases (30%) and isoechoic in 1/10 case (10%). Three out of seven (43%) of the ChRCCs lesions were hyperechoic, 2/7 lesions (29%) were isoechoic and 2/7 lesions were hypoechoic (29%).

Discrete hypervascularization could be seen in color Doppler in 2/9 CCRCCs (22%) and in 3/7 ChRCCs (43%). Except for one case (patient #21), all RCCs showed early contrast enhancement. Delayed venous wash-out could be registered in 4/9 CCRCCs (44%), in 4/10 PRCCs (40%) and in 4/7 ChRCCs (57%); in total, venous wash-out was observed in 12/26 (46%) patients with RCC.

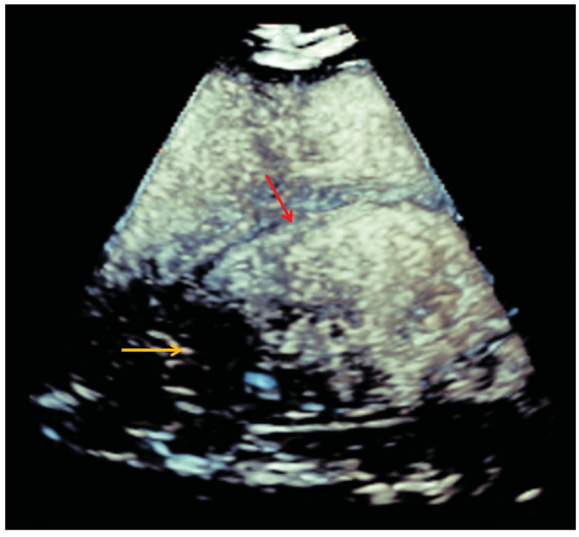

Figure 2. Venous wash-out in solitary oncocytoma of the right kidney. In patient #9, a 2.7 cm measuring renal oncocytoma of the upper pole of the right kidney shows venous wash-out in delayed phase (yellow arrow) compared to renal parenchyma (red arrow).

Discussion

Renal oncocytoma is a predominantly benign tumor, despite some rare published cases of metastasizing oncocytomas [5]. Non-invasive diagnosis of oncocytoma remains troublesome, since no reliable morphological imaging feature nor serum biomarkers yet exist.

Our findings are in line with the recent state of knowledge. So far, no CEUS feature has been delineated allowing for eligible discrimination between oncocytoma and renal carcinoma. Arterial hyper- or hypoenhancement and delayed venous wash-out are sonomorphological features that have been described in the context of renal cell carcinomas [25,26]. In synopsis with the literature, our findings implicate that CEUS does not allow for safe discrimination between renal oncocytoma and renal cell carcinoma.

In the prospective study of Gerst et al. [27], all three included oncocytomas presented as hyperechoic lesions, with two of them showing contrast enhancement with delayed venous wash-out. Haendl et al. [26] described heterogeneous echogenicity of three oncocytomas: one of them showing hypoenhancement during early and late phase, while the other lesions showed rapid contrast enhancement

Table 2. Sonomorphological features of renal cell carcinomas, control group.

Patient	Location	Size (cm)	Echogenicity (native B-mode)	Vascularization (Doppler mode)	Contrast CEUS	Histopathology
#1	Left	2.0	Isoechoic	–	+	CCRCC
#2	Right	4.0	—	(+)	+	CCRCC
#3	Left	2.5	Hyperechoic	–	+/wo	CCRCC
#4	Right	1.6	Hypoechoic	–	+	CCRCC
# 5	Right	2.5	Hypoechoic	(+)	+/wo	CCRCC
#6	Right	2.9	Isoechoic	–	+	CCRCC
#7	Left	3.0	Hypoechoic	–	+ /wo	CCRCC
#8	Right	3.0	Isoechoic	–	+	CCRCC
#9	Left	2.0	Isoechoic	–	+/wo	CCRCC
#10	Left	1.5	Hypoechoic	–	+/wo	PRCC
#11	Right	1.7	Hyperechoic	–	+/wo	PRCC
#12	Right	3.0	Hypoechoic	–	+/wo	PRCC
#13	Right	7.0	Hypoechoic	–	+	PRCC
#14	Right	2.0	Isoechoic	–	+/wo	PRCC
#15	Left	1.3	Hypoechoic	–	+	PRCC
#16	Left	5.0	Hyperechoic	–	+	PRCC
#17	Right	4.0	Hypoechoic	–	+	PRCC
#18	Right	2.3	Hyperechoic	–	+	PRCC
#19	Right	2.0	Hypoechoic	–	+	PRCC
#20	Left	1.2	Hyperechoic	(+)	+	ChRCC
#21	Right	0.9	Hypoechoic	–	–	ChRCC
#22	Right	8.0	Hyperechoic	(+)	+/wo	ChRCC
#23	Right	2.0	Isoechoic	–	+/wo	ChRCC
#24	Left	3.0	Hypoechoic	–	+	ChRCC
#25	Right	3.0	Isoechoic	–	+/wo	ChRCC
#26	Right	3.6	Hyperechoic	(+)	+/wo	ChRCC

wo, wash-out; (+), slight vascularization in Doppler mode; +, contrast enhancement in CEUS; −, negative; PRCC, Papillary renal cell carcinoma; CCRCC, clear cell renal cell carcinoma; ChRCC, Chromophobe renal cell carcinoma.

with consequent venous wash-out. Fan et al. [28] described conspicuous early hyperenhancement of one included oncocytoma. Moreover, an hyperenhancing oncocytoma in a kidney transplant recipient was recently described [29]. These diverse findings are mirrored in the present study.

In our retrospective study, the 13 included cases (12 unilateral oncocytomas, one bilateral oncocytosis) showed a varying echogenicity (46% hypoechoic, 23% hyperechoic, 8% iso-hyperechoic, 8% isoechoic), in two cases the oncocytoma only demarcated upon application of contrast medium. In the case of bilateral oncocytosis, lesions presented hyperechoic. Only 23% of the lesions showed slight vascularization in Doppler mode. We could not elucidate any oncocytoma-specific pattern of microperfusion: 85% of the renal oncocytomas presented hyperenhancing, of whom 50% also showed delayed venous wash-out. In 8% of the cases, the renal lesions featured venous wash-out in delayed phase without early hyperenhancement. Except for the case of bilateral oncocytosis (patient #8), all singular and unilateral lesions of interest presented atypical contrast-enhancement in relation to the surrounding renal parenchyma.

The heterogeneous sonomorphological appearance of oncocytic lesions is similarly reflected in that of the histological sub-types of renal cell carcinoma (CCRCC, PRCC, ChRCC). In the 26 included patients of the control group, renal cell carcinomas showed a varying echogenicity, with only five of 26 lesions featuring discrete hypervascularization in Color Doppler (Table 2).

Except for one case out of the ChRCC (patient #21), 25/26 (96%) of the included renal cell carcinoma showed early contrast enhancement, of which 12 showed, in turn, delayed venous wash-out (12/25, 48%). In one case of CCRCC (patient #2), the renal lesion only demarcated upon application of contrast medium.

In a nutshell, using native B-mode, Color Doppler and CEUS, no distinct sonomorphological feature could be registered to allow for safe differentiation between benign renal oncocytoma and the three most frequent histological subtypes of malignant renal cell carcinoma in our single-center case-control study.

The retrospective single-center nature, small patient cohort and only one radiologist evaluating renal lesions by CEUS on differing ultrasound systems are limiting factors of our study.

Our study again shows the limited predictive value of CEUS for distinguishing benign from malignant renal lesions. A relevant cohort of patients still undergoes renal surgery due to suspicious lesions that later histopathologically emerge as benign oncocytoma. The CEUS examination may add essential information to more elaborate CT and MRI scans in cases of indeterminate findings since it allows for visualization and dynamic analysis of intratumoral microperfusion in real-time with high temporal resolution at an excellent safety profile. Further research with focus on specific morphological features and reliable biomarkers of oncocytoma or rather renal cell carcinoma remains to be done.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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