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Contrast enhanced ultrasound of renal masses

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Abstract

Contrast enhanced ultrasound (CEUS) has gained clinical importance over the last years for the characterization of hepatic masses. Its role in extrahepatic indications has been investigated repeatedly but has been less comprehensively studied. Currently more than 50% of renal masses are incidentally diagnosed, mostly by B-mode ultrasound. The method of choice for characterization of renal lesions is contrast enhanced computed tomography (CECT). In the case of cystic lesions CECT refers to the Bosniak classification for cystic lesions to assess the risk of malignant behavior. The majority of masses are renal cell carcinoma, but the exact proportion is controversial. Disadvantages of CECT are a significant risk for patients with impaired renal function, allergic reactions and hyperthyroidism due to iodinated contrast agents. Several studies concerning CEUS for the characterization of both solid and cystic renal lesions have been published, but prospective multicenter studies are missing, the presented data being mainly descriptive. The aim of this manuscript is to review the current literature for CEUS in renal masses, to summarize the available data and focus on possible concepts for studies in the future.

INTRODUCTION

Ultrasound (US) is the most frequently used imaging method since it is inexpensive, has no side effects and is widely available. The majority of asymptotically diagnosed renal tumors are detected by US. Nevertheless, to date the standard method for staging purposes is contrast enhanced computed tomography (CECT). Contrast enhanced US (CEUS) has been introduced for diagnostic imaging in the liver, heart, pancreas, trauma and several other organs. Contrast agents are used for CECT and magnetic resonance imaging (MRI) techniques, and increase the sensitivity and specificity of these techniques. US contrast agents have been introduced relatively recently. They consist of microbubbles with a size similar to an erythrocyte. They resonate in the US beam and change the backscattered wave resulting in both an enhancement and a change in the waveform. This enables a selective presentation of contrast information. Both agents are usually given in a single bolus followed by a rapid saline flush intravenously, but extravascular use

has been described^[1]. Whereas SHU 508A (Levovist®), a first generation contrast agent has some affinity with the reticuloendothelial system, BR1 (Sonovue®), a second generation contrast agent is a strictly vascular contrast agent. In contrast to SHU 508A, BR1 allows real time imaging because of the higher stability of the micro-bubbles, which contain an inert gas. Studies using SHU 508A could be confirmed with BR1.

Detection and characterization of focal liver lesions are the single most important application of CEUS in the abdomen^[2,3]. CEUS now equals CECT, and in some instances exceeds it, in accuracy. Its use for renal evaluation has been less comprehensively studied. Several studies indicate also a role for CEUS in the characterization of renal masses and renal cell carcinoma (RCC) but the results are controversial^[4]. The aim of this study is to analyze the role of CEUS in renal masses referring to the literature and our own experience.

RENAL MASSES

Cancer of the kidney represents about 2% of human all cancers. In Africa and Asia the incidence is lower than in Northern America and Western Europe. The incidence and detection of asymptomatic renal masses has increased over the last 25 years - e.g. by 38% in the United States of America between 1974 and 1990. Apart from an increase in average body weight and other risk factors, this is the result of improved imaging technology as well as improved understanding of the clinical and pathological findings of RCC^[5-9]. It can be shown that the survival rate has improved over the years as a result of earlier diagnosis^[7,10-12]. To date, most (61%) renal masses are found incidentally^[13]. From the diagnostic point of view, in the case of a focal renal lesion, the following entities must be taken into account (Figure 1): neoplastic lesions, non-neoplastic lesions or masses (e.g. inflammatory, traumatic, ischemic lesions, simple and complicated non neoplastic cysts), and pseudotumors/lesions.

Neoplastic lesions can be divided into primary lesions that originate from the renal parenchyma or from the urinary system in the renal pelvis, and secondary lesions such as metastases, lymphoma, plasmocytoma, leukemia, and lesions close to the renal parenchyma e.g. urothelial/transitional cell carcinoma, adrenal lesions, and retroperitoneal lesions which mimic true renal lesions. The World Health Organization (WHO) distinguishes primary tumors of the kidney into renal cell tumors, metanephric tumors, nephroblastic tumors, mesenchymal tumors, neural/neuroendocrine tumors, hemotologic lesions, germ cell tumors.

In the following section the most frequent renal lesions (renal cell carcinoma, angiomyolipoma (AML), oncocytoma, renal adenoma) are presented. Table 1 presents an overview of rare renal tumors according to the current WHO classification.

Malignant tumors

Renal cell carcinoma: Renal cell lesions can be separated

into RCC with its several subtypes, papillary adenoma and oncocytoma. This strict pathological organization is not suitable for imaging purposes. The majority of masses seen in imaging methods consist of renal cell tumors (RCC, oncocytomas, cystic lesions), metanephric tumors (metanephric adenomas), mesenchymal tumors (AML), secondary lesions (e.g. metastases), and inflammatory lesions.

The typical triad of flank pain, hematuria and flank mass is uncommon (about 10%) and is a sign of an advanced stage of disease. Syndromes such as hypercalcemia, Stauffer syndrome, anemia, and cachexia are frequently caused by metastatic lesions or paraneoplastic syndromes^[14].

In 4%-22% of autopsied corpses small renal lesions are found which are malignant or pre-malignant. Patients are a mean of 65 years old at the time of diagnosis of RCC, and the majority is older than 40 years^[15]. In up to 20% of RCC > 3 cm, synchronous RCC are found in the same kidney. Even small tumors grow in size and metastasize and there is a benefit for the patients if they undergo surgery at an early stage^[7,16-21].

RCC are reported to grow at a rate of about 0.4 cm per year^[17,22], but this depends on the size of the lesion. In a retrospectively reviewed series of 63 consecutive patients with observational treatment for renal cancer (mean age 77 years) with a mean tumor size of 4.3 cm, there was a 5-year cancer-specific survival of 93% and an overall survival of 43%. The mean annual growth rate was < 1 cm in 85% of cases. In patients with tumors ≤ 4 cm only 4% had a growth rate of > 1 cm/year but this was significantly higher for lesions > 4 cm. The authors conclude that observational strategies for small RCC in older and comorbid patients can give acceptable results in a period of 5 years^[23].

Radical nephrectomy has been the standard for treatment of RCC. The parenchyma-sparing therapy proved to have a survival rate comparable to that for nephrectomy and is now considered to be the method of choice for small lesions. Arguments against this therapeutic approach are that 7%-11% of tumors appear multifocally and the local tumor recurrence rate is 4%-10%^[24]. The rate of multicentricity for tumors ≤ 3 cm has been shown to be less than 3%. Thus parenchyma-sparing surgery should be considered when a small tumor is confined to the renal parenchyma and is encapsulated^[25].

RCC can be divided into 4 subtypes, each developing from a different origin cell: clear cell RCC, papillary RCC, chromophobic RCC and collecting duct RCC. Clear cell RCC is the most frequent subtype of RCC. Multilocular (cystic) RCC consist entirely of cysts and the number of clear cell carcinoma cells is small whereas cysts in ordinary RCC are frequent; it cannot be distinguished from cystic clear cell RCC and should, therefore, be resected. Papillary RCC comprise 10% of RCC. Bilaterality is more frequent than in other RCC. There is a hereditary type, where multiple microscopic tumors

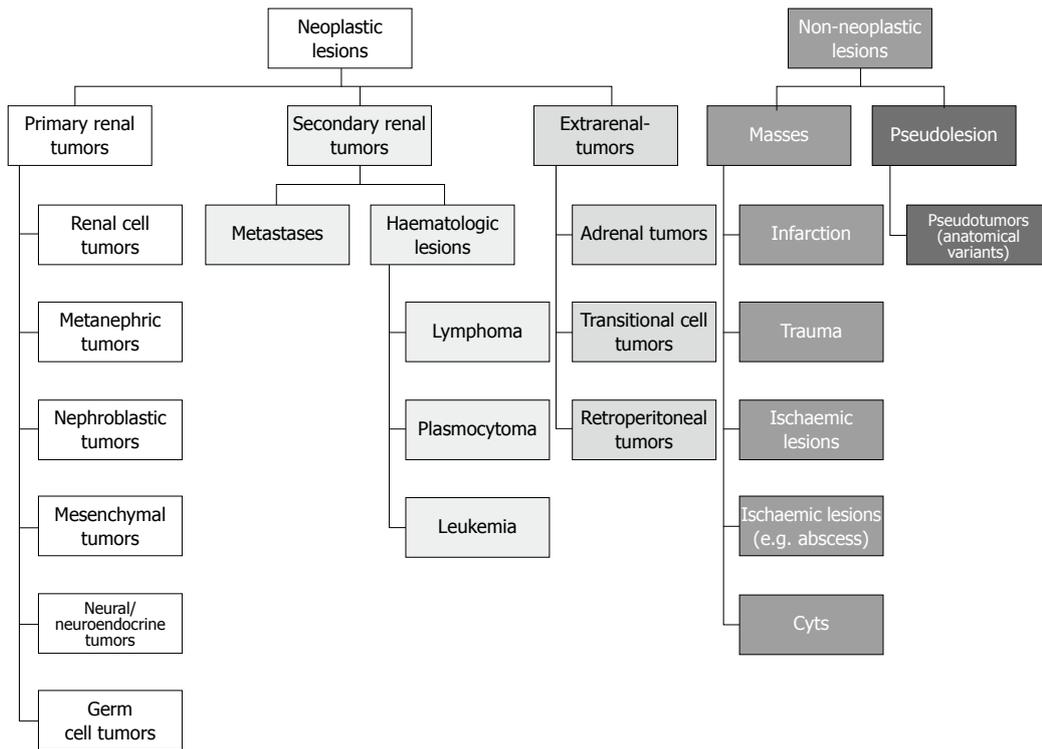


Figure 1 Differential diagnosis of renal masses.

are described. In angiographic studies, hypovascularity has been demonstrated which could be reproduced by CECT^[26,27]. Chromophobe RCC comprises about 5% of RCC. A hereditary form exists also, and most of the tumors have a good prognosis. Typically, they are large and do not show necrosis or calcification. RCC of the collecting ducts of Bellini are a rare entity. Most patients show metastasis at the time of diagnosis. Renal medullary carcinoma is a rare entity as well. Those tumors are typically seen in young people with sickle cell disease; the prognosis is poor. Other rare entities are: (1) RCC associated with Xp11.2 translocations/TFE3 gene fusions; (2) RCC associated with neuroblastoma which appear in long term survivors of childhood neuroblastoma; (3) mucinous RCC; and (4) spindle cell RCC.

Unclassified RCC appear in 5% of patients in surgical series. This category contains tumors with varied appearances and sometimes a sarcomatoid change is found.

Bilateral RCC appear in about 5% of all patients with RCC. They are hereditary in about 10% (von-Hippel-Lindau-disease, hereditary papillary RCC, hereditary clear cell RCC). Bilateral oncocytomas are described also. The survival rate is similar to that of patients with singular RCC. Metachronous lesions can appear years later^[28].

Metastases and lymphomas

Typically renal metastases are detected when a nonrenal malignancy progresses^[29], and the median survival is low when renal metastases occur^[30]. However, patients can present with a single renal metastasis without symptoms of tumor progression in follow-up investigations after a

long period of stable disease^[31,32]. Renal metastases from bronchogenic carcinoma, breast cancer, colon cancer, esophageal cancer, hepatocellular carcinoma, pancreatic adenocarcinoma, prostatic cancer, follicular and papillary thyroid carcinoma have been reported^[32-39].

Secondary renal lymphomas are 30-fold more frequent than primary renal lymphoma without evidence of systemic involvement. They are mostly present in the advanced stages of the disease. Also, a plasmocytoma can occur as a manifestation of a disseminated multiple myeloma. In contrast to RCC metastases are suggestive if they show the following imaging features: (1) < 3 cm; (2) not totally spheric, sometimes wedge-shaped; (3) signs of “infiltrative” growth; (4) bilateral multiple; (5) no encapsulation; and (6) no calcification^[40-42].

They often appear hypoenhanced in contrast enhanced studies^[29]. The group around Lassau and Lamuraglia were able to monitor the response of advanced RCC to antiangiogenetic therapy with Sorafenib in a heterogeneous group including 2/30 patients (7%) with contralateral renal metastases. Nevertheless, there was no description of the enhancement pattern in CEUS before therapy. The group suggested quantitative CEUS for monitoring antiangiogenetic drug effectiveness which has been also proposed by our group^[43]. In our experience, metastases in CEUS are typically hypovascular in more than 80% of cases. Since metastases typically do represent advanced tumor stages histologically proven elsewhere, we can only refer to one histologically proven metastasis in our patients which was hypoenhancing both in the arterial and late phase (unpublished data).

Table 1 Rare renal tumors according to the current WHO classification^[76]

Entity	Dignity	Clinical meaning
Renal cell tumors		
RCC associated with neuroblastoma	Malignant	Long term survivors of childhood neuroblastoma
Nephroblastic tumors		
Nephroblastoma	Malignant	Malignant embryonal neoplasm; 1:8000 children, 98% < 10 yr; if treated excellent prognosis = Wilm's tumor
Nephrogenic rests and nephroblastomatosis	Malignant potential	Nephrogenic rests in 1% of infant autopsies; possible transformation into nephroblastoma
Mesenchymal tumors in children		
Ossifying renal tumor of infants	Benign	12 cases reported, mostly in children < 18 mo
Clear cell sarcoma	Malignant	Typically bone metastasis, metastases can develop late
Rhabdoid tumor	Malignant	Highly invasive; 80% ≤ 2 yr; 2 yr survival rate < 20%
Congenital mesoblastic nephroma	Malignant	Excellent prognosis when completely excised; recurrence rate 5%; metastases in rare cases
Mesenchymal tumors in adults		
Leiomyoma	Benign	Arises typically from the renal capsule; incidental tumors < 10 mm, but sometimes large
Hemangioma	Benign	No mitosis and nuclear pleomorphism
Lymphangioma	Benign	Presenting as a peripelvic or renal sinus mass. Some cases may develop secondary to inflammatory lower urinary tract diseases; cystic
Juxtaglomerular cell tumor	Benign	Benign rennin-secreting tumor → hypertension; about 70 tumors described; typically < 3 cm
Renomedullary interstitial cell tumor	Benign	Common autopsy findings in adults; > 1 tumor in 50%; < 5 mm
Intrarenal Schwannoma	Benign	Common benign tumor of peripheral and auditory nerves
Cystic nephroma	Benign	Cystic; female >> male
Mixed epithelial and stromal tumor	Benign	Complex renal neoplasm; contains large cysts
Neuroblastoma	Benign	
Solitary fibrous tumor	Malignant potential	Frequent painless hematuria; confused with RCC
Paraganglioma/phaeochromocytoma	Malignant potential	
Leiomyosarcoma (incl. renal vein)	Malignant	The most common renal sarcoma; 5-yr survival rate 35%; chemotherapy is ineffective
Osteosarcoma	Malignant	
Angiosarcoma	Malignant	Rare, aggressive; poor prognosis; strong male predominance, androgen factor possible; rapid metastases
Hemangiopericytoma	Malignant	
Malignant fibrous histiocytoma	Malignant	Pararenal and retroperitoneal extension
Synovial sarcoma	Malignant	Characterized by a specific translocation: <i>t</i> (X; 18)(p11.2; q11); recurrence is commonly seen
Renal carcinoid tumor	Malignant	Association with horseshoe kidney; carcinoid syndrome < 10%; cystic, calcification
Neuroendocrine carcinoma	Malignant	Poorly differentiated epithelial NPL with neuroendocrine differentiation; poor prognosis; necrotic mass
Primitive neuroectodermal tumor (Ewing sarcoma)	Malignant	Inhomogeneous, often replacing the entire kidney; hemorrhage, necrosis
Plasmocytoma, Lymphoma and Leukemia		
Lymphoma	Malignant	Typically secondary renal lymphomas; primary renal lymphoma very rare
Plasmocytoma	Malignant	Occurs as a manifestation of a disseminated multiple myeloma
Leukemia	Malignant	Interstitial infiltration of leukemic cells can be called extramedullary leukemia in the kidney
Germ cell tumors		
Teratoma	Benign	
Choriocarcinoma	Malignant	Difficult to differentiate from high grade urothelial carcinomas; mostly metastases from testicular germ cell tumors

RCC: Renal cell carcinoma; NPL: Neoplasia; >>: Much more frequent or predominantly seen in female.

Metastases in the kidney appear in advanced tumor stages and should be expected in the case of a hypoenhancing mass and/or evidence of a primary tumor. Biopsy can be discussed to rule out a secondary malignancy if this leads to therapeutic consequences. The evidence in the CEUS literature is rare.

Benign renal tumors

Angiomyolipoma (AML): The prevalence of AML (hamartomas) reported in the literature varies from

0.03%-0.07%^[44]. They are composed of a variable proportion of adipose tissue, spindle and epithelioid smooth muscle cells and abnormal thick-walled blood vessels. AML can occur in patients with tuberous sclerosis. They belong to a family of lesions characterized by proliferation of perivascular epithelioid cells (PEC). Clonality could be shown. There is onset of AML after puberty as well as a progesterone receptor immunoreactivity in AML. Synchronous occurrence with oncocytomas or with RCC has been described. Vascular extension up to

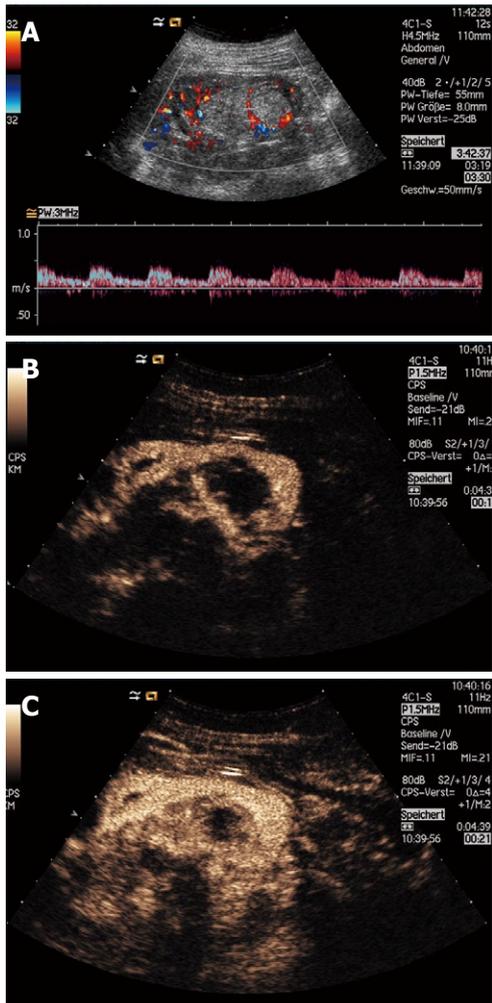


Figure 2 Histologically proven angiomyolipoma with typical central artery (which has been also described in some oncocytoma). Doppler US analysis reveals a relatively low resistance index (A); In CEUS the lesion shows a hypovascular enhancement (B, C).

the vena cava has also been reported, as well as 3 cases of sarcoma arising in AML^[45-47]. Small precursor lesions consist of epithelioid smooth muscle cells whereas the proportion of adipocytes and spindle cells increase when they grow. Some rare cases are associated with spontaneous hemorrhage in lesions > 4 cm and in pregnant women. Epithelioid AML is a malignant variant. More than 50% of patients with epithelioid AML have tuberos sclerotic; the typical patient is 35-40 years old, and one-third suffer from metastatic disease at the time of diagnosis. Patients frequently present with pain. The tumors show typically a poor fat content, therefore, in imaging techniques they are rarely confused with classic AML.

AML are lesions which are frequently found in screening investigations. In patients investigated at our hospital the typical sonographic findings of AML were found in about 1% of 10000 consecutive patients (unpublished data). Diagnosis using unenhanced CT is possible in most patients with respect to demonstration of fat equivalent density. AML represents a diagnostic challenge for every imaging method in case of hemorrhage,

calcification, arteriovenous shunts (“highly vascular AML”), necrosis, and low fat content^[48,49].

Up to 14% of all AML are wrongly diagnosed with CECT leading to unnecessary surgery. Papillary RCC can mimic AML with low fat appearance with homogeneous enhancement and slow washout^[50]. Some authors suggest nephron-sparing surgery in the case of calcified lesions^[51-53]. In US they show a typical snowball-like pronounced hyperechoic appearance. Up to 25% of small RCC are hyperechoic in comparison to the surrounding renal parenchyma (own unpublished data). Atypical only slightly hyperechoic AML are found in 30%, and iso- or hypoechoic variants in 6%.

Some reports focused on the fat content in renal cell carcinomas^[54-57]. In particular, fat containing renal tumors can also be lipomas, liposarcomas, and oncocytomas^[58]. Several reasons have been discussed, such as lipid producing necrosis, intra-tumoral bone metaplasia containing fatty marrow elements, and entrapment of perirenal or sinus fat^[57-59].

In CEUS, AML appear typically as hypoenhancing with a progressive hypoenhancement in the late phase (Figure 2^[60-62]). In other studies, AML showed a wide range of enhancement patterns without sharp discrimination in comparison to RCC^[63].

The typical AML can be diagnosed with satisfying accuracy by unenhanced CT. Up to 14% of all AML are atypical and can lead to unnecessary surgery, especially when hemorrhage, calcification, arteriovenous shunts, necrosis or low fat content appears. RCC or oncocytoma can also contain fatty components. In CEUS, AML are typically less enhancing than RCC but there are overlaps in the CEUS appearance.

Renal adenoma: In the literature the concept of renal adenoma is controversial. The current WHO classification only describes papillary and metanephric adenomas, of which papillary adenomas are < 5 mm and, therefore, do not play a significant role in imaging of renal masses. All renal tumors of the clear cell type are considered malignant^[64] since malignant transformation of renal adenomas have been described and genetic predictors of the transformation are unknown^[5,27,65-68]. Papillary adenomas are tumors with low nuclear grade, show no mitotic figures and are ≤ 5 mm. In autopsy studies they are found in 10% of patients < 40 years old and in 40% of patients > 70 years old. They are typically located below the renal capsule. They can be multiple and bilateral. Multiloculated adenomas are called renal adenomatosis. Metanephric adenoma, adenofibroma and stromal tumors are rare benign neoplasia with similar features occurring at different ages. Metanephric stromal tumors appear only in children, metanephric adenofibroma in children and young adults and metanephric adenomas in the young and old. One single case of a high grade sarcoma in association with metanephric adenoma has been reported^[69]. An association of metanephric adenomas with Wilm’s tumor or RCC has been described^[70].

There are only a few reports on progression of these tumors^[66,69]. Typically they have a size of 3-6 cm and are well circumscribed. Hemorrhage and necrosis are common. Twenty percent show calcification, as well as small cysts.

In studies using CEUS, metanephric adenomas appeared in only 2 patients of 2 different studies from the same group^[60,61]. The contrast enhanced features revealed hyperenhancement in the arterial phase but progressive hypoenhancement in the late phase. Our own data revealed one metanephric adenoma which showed a rim enhancement with hypovascular appearance in the arterial and in the late phase.

Adenoma histology in renal tumors is rare. There is evidence for malignant transformation in some variants. Papillary adenoma is ≤ 5 mm. Metanephric adenomas have no specific imaging features either in CECT or in CEUS.

Oncocytoma: Histologically, oncocytomas are composed of large cells with mitochondria-rich eosinophilic neoplasm, and originate from intercalated cells of the distal renal tubules. The entity was first described by Zippel in 1942. Oncocytosis or oncocytomatosis is a syndrome with oncocytic tumors, oncocytic changes in benign tubules, microcysts lined by oncocytic cells and clusters of oncocytes within the renal interstitium^[64,71]. In the current WHO classification, oncocytomas are considered as benign lesions. Nevertheless there is an ongoing discussion on cases of oncocytomas developing metastases^[72].

Oncocytomas are difficult to differentiate pathologically from an eosinophilic variant of chromophobe RCC which itself is considered to have low malignant potential. In a study by Breda *et al.*^[73] a chromophobe RCC was diagnosed via biopsy as an oncocytoma, and an oncocytoma was diagnosed via biopsy as a chromophobe RCC. In a case of oncocytosis, a hybrid oncocytoma/chromophobe RCC lesion was identified by Al-Saleem *et al.*^[74]. The literature concerning the rate of metastatic oncocytomas is weak, in some instances sometimes lacking histological confirmation of the oncocytoma origin of the metastases, and sometimes the oncocytoma diagnosis was questionable^[72,75]. A review of non-urothelial renal tumors revealed 70/954 oncocytomas (7%)^[76], of which 1/70 had an asymptomatic liver metastasis confirmed by needle biopsy.

In imaging, the diagnosis can also be difficult. Choudhary *et al.*^[77] investigated CECT imaging features in 21 patients with 28 histologically confirmed oncocytomas. The lesion size ranged from 1.2-12 cm, mean 4.9 cm. In all lesions contrast enhancement could be detected. In 64% the enhancement was isodense and in 36% the enhancement was hypodense in comparison to the renal cortex. In 5/28 lesions (18%) a central scar could be identified pathologically, but was detected by CECT only in 3/28 lesions (11%, lesion size 10-29 mm). The authors concluded that imaging features fail to demonstrate typi-

cal features in oncocytomas. The often discussed central scar is seen histologically in 18%-33% of tumors and correlates with the size of the lesion^[64,77]. It can be confused with areas without enhancement in RCC (own data: 69% in 300 histologically proven RCC, 40% of 20 lesions published by Wink *et al.*^[78]). Correlation of this sign with tumor size has been published^[79]. Therefore, the central scar sign lacks specificity as well as sensitivity. In the CEUS literature, the perfusion pattern in patients with oncocytomas is described by the group around Strobel^[4]. They found a stellate scar in none of 3 oncocytoma, 2 of 3 (67%) were hypervascular in the arterial phase, 1 of 3 (33%) was hypovascular. In the late phase all were hypoenhancing compared to the surrounding renal parenchyma. Tamai *et al.*^[80] evaluated 29 patients with CEUS, 2/29 (7%) had an oncocytoma. In 50% of patients with an oncocytoma, a spoke-like enhancement pattern could be demonstrated with CEUS in contrast to CECT. Fan *et al.*^[62] reported that there were no characteristic patterns in one patient with oncocytoma.

Oncocytomas are benign lesions. Typical but rare signs for oncocytomas are a spoke-like enhancement and a central scar. Nevertheless neither in CECT nor in CEUS can both signs be displayed regularly, and positive and negative predictive values are low. We suggest discussing a biopsy in lesions with typical oncocytoma appearance. Histological diagnosis is also difficult.

Renal pseudotumors: Pseudotumors are mass-like anatomical variations without pathological significance. Besides fetal lobation, dromedary or splenic humps, a proportion of pseudotumors is caused by hypertrophied columns of Bertin. Those represent unresorbed polar parenchyma of one or both of 2 subkidneys that fuse to form a normal kidney and contain renal cortex, pyramids, and columns (septa) of Bertin. It can be referred to as junctional parenchyma^[81,82]. In clinical practice, the ability of US and CECT to distinguish between anatomical variations and real neoplasia is frequently challenging. Typical US features are: (1) location between the overlapping portion of 2 renal sinus systems; (2) clear definition from the renal sinus; (3) a size < 3 cm; (4) comparable echogenicity to the renal parenchyma; (5) the structure is bordered by a junctional parenchymal line; and (6) the demonstration of regular/branch-like renal blood flow in the suspected lesion^[83].

Ascenti *et al.*^[84] described their experience with contrast enhanced power Doppler with SHU 508A in 4 patients with renal pseudotumors. They could differentiate those changes from real neoplastic disease^[84]. In more than 300 patients with renal masses investigated prospectively with US, color Doppler US (CDUS) and CEUS at our institution there were 4% histologically proven pseudotumors which could be reliably differentiated from real neoplasm. Neoplasia could not be ruled out with CECT. Nevertheless follow-up investigations must be performed in certain cases. Several other investigators have stressed this issue also^[62,63,85-90].

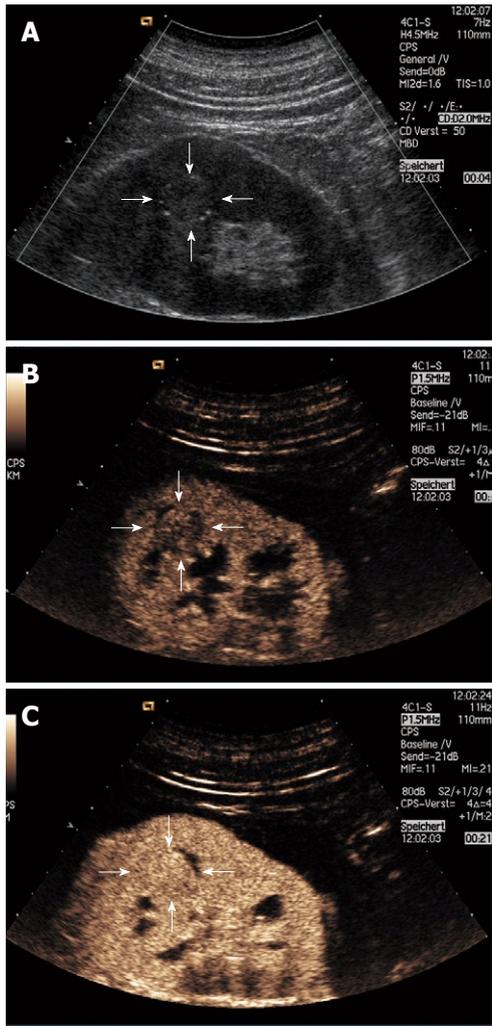


Figure 3 Small renal cell carcinoma (13 mm) not detectable by computed tomography (CT); B-mode reveals an isoechoic lesion without mass effect (A); contrast enhanced ultrasound (CEUS) in the arterial phase showed the lesion slightly hypoechoic (B) and after 33 s isoechoic (C); 2D Video shows the transcutaneous biopsy proving clear cell renal cell carcinoma; consecutively the patient underwent surgery.

In the diagnosis of pseudotumors with US there are different B-mode and CDUS criteria. If in CEUS a normal perfusion pattern can be distinguished, this represents a major criterion for the diagnosis of a pseudotumor. Published evidence is limited.

DETECTION OF RENAL MASSES

The accuracy of conventional B-mode alone, or in combination with CDUS in the detection and characterization of renal masses, is considered to be less reliable than other imaging techniques^[91]. This is especially true if they are not contour deforming^[16]. Jamis-Dow *et al*^[6] reported detection rates for lesions < 30 mm, < 20 mm, and < 10 mm of 99%, 95% and 76%, respectively, for CECT. For US the rates were 95%, 70% and 20%, respectively. In more recent studies this is controversially discussed. Sixty patients with renal masses were investigated by Spahn and co-workers to assess the ability of CDUS for staging

purposes in comparison to CECT and surgical findings which served as reference methods^[92]. The sensitivity of CDUS for tumor detection and detection of lymph node metastases was 100%. CDUS was superior to CECT in the detection of renal vein involvement. In a study of Dong *et al*^[93] the detection rate with conventional US in 42 patients with clear cell RCC (1.8-11.2 cm) was 30/42 (71%), which could be improved by CEUS to 100%. The size distribution of the lesions is not shown in the article whereas 33/42 lesions (78%) are referred to as “larger tumors”. We must admit that the results were not in accordance with our own experiences. In 143 patients with renal masses submitted to our hospital with available histology and accessible CECT imaging there were 3/143 lesions (2%) with a < 15, 25 and 25 mm which were not detected in CECT but were detected in CEUS (unpublished data, Figure 3).

A major advantage of US in comparison to other imaging techniques is its ability in the characterization of cystic lesions. CECT sometimes fails to differentiate cysts containing blood or fluids with high protein content and, therefore, elevated density (in comparison to water). The detection of blood flow is a major issue in the detection of renal masses. Kitamura *et al*^[94] evaluated the ability of CDUS in comparison to CECT in the staging of renal solid tumors. They investigated 110 patients with lesions < 7 cm. In 9/110 patients (8%), CECT showed enhancement in the cortical nephrographic phase whereas CDUS showed no flow. In 8/110 patients (7%), CDUS showed flow whereas CECT showed poor enhancement. Thus it can be concluded that CDUS has an accuracy for detection equal to CECT.

US (performed by a sophisticated investigator) has a detection rate comparable to that of CECT but the evidence is sparse. In the detection of blood flow in renal lesions CDUS, it has comparable sensitivity to CECT. CEUS is more sensitive than CDUS in the detection of blood and has been shown to be superior to CECT in a limited number of patients. Published data are limited.

The majority of renal masses are incidentally detected nowadays. The major issue for each imaging method is to characterize lesions when this leads to a therapeutic impact. For CEUS, this could be shown for liver lesions^[95] or pancreatic lesions^[96].

In contrast to liver or pancreas tumors, the characterization of renal tumors is more difficult. There is a small and heterogeneous proportion of benign lesions. Surgery is believed to be the method of choice for each solid renal lesion because of the high rate of malignancy. So most studies for characterization of renal masses with CEUS did not focus on the characterization but on the staging of renal masses with US. In the more recent literature this strategy is questioned. Particularly in small lesions (< 4 cm), the proportion of benign lesions has been reported to be higher than 13%^[97-102] and histology obtained by transcutaneous biopsy is reliable and can be safely performed. An analysis of the literature for the proportion of benign lesions is given in Table 2.

Table 2 Frequency of benign lesions in consecutive patients

Author	n	Benign	Angiomyolipomas	Oncocytomas	Metanephric adenomas	Atypical cysts	Others	Population
[103]	396	5%			1% ⁷		2% ⁸	Surgery
[104]	30	17%	13%			3%		Ultrasound
[105]	70	26%	1%	4%		14%	7% ³	Biopsy
[106]	40	23%	10%			13%		Ultrasound
[107]	35	17%	3%			10%	3% ¹	Surgery
[108]	173	14%	4%	8%		2%		Surgery
[109]	20	35%	5%	5%			25% ²	Surgery
[110]	78	21%	3%	17%				Biopsy
[111]	26	21%	8%	12%				Biopsy
[60]	26	31%	27%		4%			Ultrasound
[80]	29	10%	3%	7%				Ultrasound
[61]	23	34%	30%		4%			Ultrasound
[112]	54	21%	4%	11%		6%		Biopsy
[113]	97	25%	25%					Ultrasound
[4]	30	10%		10%				Ultrasound
[114]	99	7%	1%	6%				Surgery/Biopsy
[115]	543	15%	5%	6%	0.2%		3% ⁴	Surgery
[73]	31	13%		10%			3% ⁵	Surgery
[59]	100	20%	3%	13%	2%		2% ⁶	Biopsy
[64]	954	7%		7%				Surgery
[100]	2770	13%						Surgery
[78]	18	33%	11%			22%		Ultrasound
Own data (unpublished)	143	15%	3%	1%	1%	1%	8% ⁹	Ultrasound

Data are given as percentage; N indicates the total number of included patients. ¹Leiomyoma; ²1 abscess, 1 lesion associated with xanthogranulomatous pyelonephritis, 2 cysts, 1 arteriovenous fistula; ³1 lesion associated with xanthogranulomatous pyelonephritis, 3 lesions associated with chronic pyelonephritis, 1 lesion associated with tuberculosis; ⁴Leiomyoma 0.9%, papillary adenoma 0.6%, abscess 0.4%, haematoma 0.4%, giant cell fibroblastoma 0.2%, lipoma 0.2%, haemangioma 0.2%; ⁵Benign lymphoid infiltrate; ⁶Mixed epithelial and stromal tumor; ⁷Adenoma, not further specified; ⁸Haemangioma 1%, cystic nephroma 0.5%; ⁹Abscess 2%, pseudotumour 4%,focal cystic dysplasia 1%, necrosis 1%.

Renal mass biopsy

Since there is a significant proportion of lesions with benign diagnosis especially in small lesions (Table 2), several studies reported on percutaneous renal mass biopsy guided either by CECT or US. In the analysis of the literature the rates for benign lesions were between 5% and 34% (Table 2). The question, which needle size to use was discussed by Breda *et al*^[73]. They investigated intraoperatively 27/31 RCC (87%), 21/31 clear cell RCC (68%), 3/31 papillary RCC (10%), 3/31 chromophobe RCC (10%), 3/31 oncocytomas (10%), 1/31 benign lymphoid infiltrates (3%) with 14, 18 and 20 G core needle biopsies each after extirpation. They found a correlation of biopsy findings with final histology in 94%, 97% and 81%, respectively. They suggest 18 G to be a suitable size for renal biopsy. Wang *et al*^[59] investigated the sufficiency and accuracy of percutaneous core biopsy in renal masses < 4 cm performed with CT or US guidance (60% vs 40%). A total of 110 biopsies were performed, of which 100/110 (91%) were sufficient. Histology revealed 35% benign lesions (Table 2). 8/110 complications (7%) were reported (1 hypotension, 2 hematomas without intervention, 4 patients with severe pain and 1 with wound infection). In 34 patients biopsy could be compared with final surgical histology, and the accuracy was 100%^[59]. Shannon *et al*^[116] investigated renal core biopsies of 222 lesions < 5 cm with respect to accuracy in comparison with surgical histology. The rate of diagnostic biopsies was 78%; 25% of the lesions were benign. The accuracy

rate in comparison with final surgical histology was 100%. Significant complications appeared in 0.9% of patients. Kramer *et al*^[117] report on their retrospective analysis of intraoperative biopsies before surgical cryoablation of renal tumors. There were 81/119 patients (68%) in which one core was taken, 38/119 patients (32%) had 3 cores taken. In the “one core group” 49/81 (60%) were malignant and 14/81 (17%) were not diagnostic. In the “3 core group” 27/38 (71%) were malignant (*P* = 0.25) and 2/38 (5%) were not diagnostic (*P* = 0.03). To increase the number of diagnostic biopsies it is reasonable to project this strategy to percutaneous biopsies, but there are no data concerning safety/complications.

As there is a significant proportion of benign lesions there is a need for preoperative histological analysis in selected cases. The reported rates for diagnostic biopsy range from 75% to 100%. It could be shown that at least 18 G core biopsies should be used from a histopathological standpoint but data concerning complications following multiple biopsies are not available. It could be also proven that 3 cores in one patient are more sufficient than one biopsy. This could not be shown for percutaneous biopsies for ethical reasons.

Differential diagnosis of solid renal tumors on US

Unenhanced US: Since B-mode US lacks specific characteristics to differentiate benign and malignant renal masses, CDUS characteristics were investigated in several settings. Habboub *et al*^[118] could demonstrate renal

mass perfusion using CDUS in 42 of 44 patients (95%). In 60 patients with renal masses which were investigated by Spahn and co-workers, equal results were found with CECT and surgical findings^[92]. Kitamura *et al*^[94] evaluated the ability of CDUS in comparison to CECT in the staging of renal solid tumors. They investigated 110 patients with lesions < 7 cm. In 9/110 (8%) patients CECT showed enhancement in the cortical nephrographic phase whereas CDUS showed no flow. In 8/110 (7%) patients CDUS showed flow whereas CECT showed poor enhancement. The authors concluded that CDUS has a diagnostic accuracy equal to CECT. The detection of blood flow in renal solid tumors using CDUS and/or power Doppler US as a predictor for clear cell RCC histology was investigated by Raj *et al*^[103]. Any flow that was detected with the methods mentioned above was defined as vascular flow. The authors did not give information about the CD settings. Two hundred and ninety nine patients were retrospectively analyzed and 97 patients were analyzed prospectively. The proportion of benign lesions for the retrospective and prospective groups were 4% and 7%, respectively, with a calculated rate of 5% for both groups. There was a strong association of vascular flow with clear cell RCC histology.

Unenhanced CDUS has a detection rate for blood flow comparable to CECT, whereas CEUS is superior to CECT. A characterization of benign and malignant lesions is not possible with satisfying accuracy using CDUS, CEUS or the traditional reference standard CECT.

Contrast enhanced ultrasound: Since the availability of US contrast agents, several studies have been performed for the characterization and staging of solid renal lesions (Figure 4). CEUS is always performed after conventional B-mode US and must, therefore, be regarded as a combination of both methods.

As early as 1994 Filippone *et al*^[104] described contrast enhanced CD flow imaging with a high mechanical index and SHU 508A in 30 patients with 22/30 RCC (73%), 1/30 sarcoma (3%), 1/30 leiomyosarcoma (3%), 1/30 urothelial cell carcinoma (3%), 1/30 hemorrhagic cyst (3%) and 4 AML (13%). They found CD signals inside the lesion with conventional CDUS and CEUS in 13/30 (43%) and 26/30 (87%) patients, respectively.

Ascenti *et al*^[84] demonstrated a sufficient diagnosis of renal pseudotumors with contrast-enhanced power Doppler US using SHU 508A in 4 patients. The same group performed contrast enhanced power Doppler with SHU 508A in 32 patients with 41 lesions (26 AML, 11 RCC, 3 pseudotumors, 1 metastasis) with hyperechoic lesions to evaluate its ability in the differential diagnosis of RCC *vs* AML. All malignant lesions were diagnosed histologically, all benign lesions with CECT or follow-up. In most cases, RCC showed peripheral and central enhancement, and AML showed a wide range of different patterns of vascularity. With CDUS a correct diagnosis could be found in 76%, which could not be improved by injection of SHU 508A^[63].



Figure 4 Renal cell carcinoma (T1), incidentally detected. CEUS investigation 12 s after injection of 2.4 mL BR1 (SonoVue®).

Quaia *et al*^[60] investigated 23 lesions, including 15/23 RCC (65%), 1/23 metanephric adenoma (4%) and 7/23 AML (30%). With SHU 508A, heterogeneous behavior in the arterial phase was typical for RCC. The results in the late phase were not homogeneous. AML showed peripheral hypovascularity compared to renal tissue. Six of 7 AML were diagnosed by CT, all other tumors by histology.

In 2004, Tranquart *et al*^[119] reported on their experience with the investigation of 18 patients with different focal and diffuse renal diseases using BR1 (SonoVue®) and contrast specific software. CECT or magnetic resonance imaging was used as the reference method. Compared to conventional B-mode US, they found a better tumor delineation, a better detection of venous extension and a better characterization of cystic masses.

The group around Siracusano and Quaia investigated 23 patients with renal masses using SHU 508A with contrast specific software^[61]. CECT diagnosis or histology was used as the reference method. Results were solid RCC in 11/23 (48%), 7/23 AML (30%), 4/23 cystic RCC (17%), 1/23 metanephric adenoma (4%). Solid RCCs had a higher contrast enhancement than AML. The benign lesions showed a progressively decreasing enhancement in the delayed phase.

Kabakci *et al*^[120] investigated 21 patients with RCC using conventional power Doppler and contrast enhanced power Doppler US with SHU 508A and correlated their findings with microvessel density. Microvessel density has been shown to be a significant prognostic factor in a subgroup of patients with low tumor stages. They found a significant correlation between color pixel ratio in conventional power Doppler and contrast enhanced power Doppler US and microvessel density.

Tamai *et al*^[80] evaluated the usefulness of CEUS in the diagnosis of solid renal tumors. They included 29 patients who were investigated with conventional B-mode US and whose tumors were surgically resected. The histological diagnoses were RCC in 25/29 (86%), urothelial cell carcinoma in 1/29 (3%), oncocytomas in 2/29 (7%) and AML in 1/29 (3%) patients. CECT, here a multidetector scanner, failed to detect tumor blood flow in 5/29 patients (17%), while CEUS demonstrated flow in 29/29

(100%). In 1 of 2 patients with oncocytomas, a spoke-type enhancement pattern could be demonstrated with CEUS in contrast to CECT.

The group around Lassau and Lamuraglia reported on the experience with dynamic contrast enhanced Doppler US as a predictor of tumor response. They investigated a relatively heterogeneous group of 30 patients treated with Sorafenib for metastatic renal cell carcinomas [8/30 (27%) patients with lymph nodes involvement, 8/30 (27%) with liver metastases, 3/30 (10%) with recurrent renal lesions, 3/30 (10%) with adrenal metastases, 2/30 (7%) with contralateral renal metastases, 1/30 (3%) with pancreas metastases as well as more than one metastatic location in 5/30 (17%) patients]. They suggested quantitative CEUS for monitoring antiangiogenic drug effectiveness in renal cancer^[43].

Kawata *et al.*^[121] reported on 6 patients with recurrent RCC and demonstrated the utility of CEUS in this subgroup. In 5/6 patients (83%) the lesions were detected with conventional US, in 1 patient the diagnosis could only be made with CEUS.

Wink *et al.*^[78] examined 18 patients with renal masses using CEUS with BR1. Inhomogeneous enhancement was typical for RCC. In 4/10 patients (40%) with histological analysis, CEUS demonstrated areas without enhancement which correlated with necrosis pathologically. Fan *et al.*^[62] investigated 72 patients with renal lesions \leq 5 cm with contrast specific software and BR1 (Sonovue[®]) [44 RCC (61%), 24 AML (32%), 2 hypertrophied columns of Bertin (3%), 1 oncocytoma (1%), and 1 abscess (1%)]. The rates of histological confirmation for RCC, AML, oncocytoma, hypertrophied columns of Bertin and abscesses were 100%, 17%, 100%, 0% and 0%, respectively^[62]. They found hyperenhancement in the late phase to be predictive for RCC (sensitivity 77%, specificity 96%). Also heterogeneous enhancement was characteristic for RCC. AML were homogeneously enhancing with hypoenhancement in both the arterial and late phase.

Jiang *et al.*^[79] correlated CEUS features of 92 pathologically confirmed clear cell RCC in relation to tumor size. The degree of enhancement showed no correlation, but the homogeneity of enhancement correlated with tumor size. In tumors \leq 3 cm, homogeneous enhancement was seen in 72% in contrast to tumors $>$ 3 cm (9%). In patients with tumors \leq 2 cm, a pseudocapsule appeared in 3/13 cases (23%), in tumors from $>$ 2 to 5 cm in 38/58 cases (66%) and in tumors $>$ 5 cm in 5/21 cases 24%. Inhomogeneous enhancement correlated with necrosis or cysts by histological analysis. A pseudocapsule was histologically diagnosed in 46/92 of the lesions (50%) and correlated with a rim of perilesional enhancement in 42/46 patients (91%).

Dong *et al.*^[93] characterized 42 patients with histologically proven clear cell RCC using time intensity curves received from video frames of second harmonic imaging with BR1. They could not differentiate a characteristic pattern. In time intensity curves, clear cell RCC had a

time to peak enhancement shorter than that of normal renal parenchyma and the mean value of the descent slope rate was lower. Avascular areas or filling defects were predominantly seen in larger tumors (33/42 (78%).

Thirty patients with solid renal tumors were investigated by the group around Strobel and Bernatik^[4]. RCC had a size of 65.4 ± 6.5 mm and were hypoechoic, isoechoic and hyperechoic in 52%, 36% and 12%, respectively. RCC showed a chaotic vascular pattern except for one lesion which was cystic and showed no enhancement at all. Hyperperfusion, isoperfusion and hypoperfusion was seen in the arterial phase in 12/25 (48%), 3/25 (12%) and 9/25 (36%), respectively. In the late phase hyperperfusion, isoperfusion and hypoperfusion was seen in 5/25 (20%), 9/25 (36%) and 10/25 (40%), respectively. The authors conclude that CEUS is not useful in the characterization of small renal masses.

Our group investigated more than 300 patients referred for surgical treatment of a renal mass. We performed conventional B-mode and color/power Doppler US as well as CEUS with BR1. In the majority of our patients histology was obtained by surgery (87%); in the other patients histology was obtained by biopsy (13%). Four percent of patients had lesions which finally proved to be of extrarenal origin, a proportion which is in accordance with the literature^[105]. Overall there were 15% benign lesions, 22% of lesions $<$ 40 mm had benign histology and 10% of lesions \geq 40 mm had benign histology. In 77% of patients with histologically determined RCC, 9% were cystic. CEUS could predict malignancy with a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 97%, 45%, 91%, 75%, and 90%, respectively. CEUS (CECT) had a sensitivity, specificity, positive, negative predictive value and accuracy of 85% (38%), 97% (98%), 72% (63%), 98% (94%), and 96% (92%), respectively, for vein invasion. The correct staging was diagnosed by CEUS (CECT) in 83% (69%). The interpretation of the mentioned results favored CEUS in comparison to CECT for staging and characterization of RCC.

The majority of clear cell RCC are hypervascular. One third of papillary RCC are hypovascular, although this does not lead to immediate consequences. A significant proportion of RCC show unenhanced areas which correlate with necrosis in histology. A significant pattern for RCC which leads to sharp discrimination between RCC and benign lesions cannot be currently defined.

Staging of renal cell carcinoma with CEUS

Staging parameters in RCC are of prognostic importance. In early stage RCC, partial nephrectomy is recommended. The 5-year survival rate after radical nephrectomy is reported to be between 75%-95% for patients with organ confined disease and 0-5% for patients with metastatic disease at time of presentation^[122]. In locally advanced RCC (T \geq 3, N0 and M0) certain subgroups (especially T2 and T3a) differ significantly in survival rates^[123]. In contrast to preoperative T3a staging, detection of

stages T3b and T3c is crucial since it influences the surgical approach. Renal vein invasion occurs in about 4%-10% of RCC^[124,125]. Habboub *et al*^[118] investigated the usefulness of CDUS in the assessment of venous invasion in RCC. The rate of venous invasion was 16/37 (43%), CDUS had a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 75%, 96%, 92%, 85%, and 87%, respectively, for renal venous involvement, in 2 false positive cases the intrarenal veins were involved. The detection rate for inferior vena cava involvement was 100% accurate. Bos and co-workers found that vein invasion was correctly staged in 93% with conventional B-mode US including CD and in 86% with CECT^[126]. Sixty patients with renal masses were investigated by Spahn *et al*^[92] to assess the ability of CDUS for staging purposes in comparison to CECT and surgical findings. The sensitivity for CDUS for tumor detection and detection of lymph node metastases was 100% (golden standard CECT). CDUS was superior to CECT in the detection of renal vein involvement. Gupta *et al*^[127] compared CECT, MRI and CDUS for the detection of venous invasion in RCC. They investigated 59 patients with RCC and venous involvement, CDUS showed comparable results to CECT and MRI. Kitamura *et al*^[94] evaluated the ability of CDUS in comparison to CECT in the staging of renal solid tumors. One hundred and ten patients with lesions < 7 cm were investigated. In 9/110 (8%) patients, CECT showed enhancement in the cortical nephrographic phase whereas CDUS showed no flow. In 8/110 (7%) patients, CDUS showed flow whereas CECT showed poor enhancement. The authors concluded that CDUS had a diagnostic accuracy equal to CECT.

In recent studies, the role of tumor pseudocapsule in the staging of RCC is discussed. RCC generally do not have a true histologic capsule. A pseudocapsule results from tumor growth producing ischemia and necrosis of adjacent normal parenchyma. It is composed of fibrous tissue and compressed renal parenchyma. This pseudocapsule is not described in the TNM classification^[128] but is a pathologic feature frequently seen in early stage, low-grade RCC. It is a useful sign in the differential diagnosis of RCC and in the choice for a nephron sparing surgical approach. In MRI the pseudocapsule appears as a hypointense rim surrounding the tumor on T2-weighted images. In conventional B-mode US a pseudocapsule appears as a peritumoral hypoechoic halo. Ascenti *et al*^[106] investigated the ability of second harmonic imaging using BR1 to detect a pseudocapsule in 32 patients with 40 renal masses [5/40 hemorrhagic cysts (13%), 4/40 AML (10%), 4/40 lymphoma (10%), 1/40 metastasis (3%), 26/40 RCC (65%)]. A pseudocapsule was correctly diagnosed in 12/14 histologically evaluated RCC (86%). In the other 12 renal cell carcinomas, a pseudocapsule was not found histologically. In all other lesions a pseudocapsule was not visible. The benign lesions were diagnosed with CT or MRI. The positive predictive value was 100% but the negative predictive value was below 50%^[106].

Jiang *et al*^[79] correlated CEUS features of 92 pathologically confirmed clear cell RCC in relation to tumor size. In patients with tumors ≤ 2 cm, a pseudocapsule appeared in 3/13 cases (23%), in 38/58 cases (66%) with tumors from > 2 to 5 cm and in 5/21 cases (24%) with tumors > 5 cm.

Staging for RCC can be performed with CEUS accurately with a diagnostic accuracy comparable to CECT. Even CDUS seems to have a high sensitivity, particularly if there is renal vein involvement. A pseudocapsule is a feature only seen in RCC; it indicates an early stage and can be seen in about 23%-66% of lesions. In CEUS a perilesional hypervascular rim can be seen with an accuracy of about 85%. The sign has a high positive predictive value, but the role of the pseudocapsule has not been defined in current TNM classifications.

Assessment of local ablation therapy for renal cell carcinomas

Local ablation therapy either with cryotherapy or radiofrequency ablation can be used for curative treatment of RCC. Wink *et al*^[129] suggested CEUS for monitoring of cryotherapy as a curative treatment for patients with RCC < 4 cm. They presented a CEUS investigation which enabled easy identification of the lesion before and after treatment. They found the selective detection of contrast resulting in high accuracy for the diagnosis of flow *vs* no flow most helpful.

Since CEUS is the imaging method with the best separation of tissue and contrast signal and since US contrast agents stay strictly in the vascular bed it is mostly suitable for questions of vascularity and/or necrosis. There are preliminary data showing comparable results to reference imaging methods like CECT and MRI after radiofrequency ablation or cryotherapy of renal cell carcinomas.

Characterization of cystic lesions with CEUS

Cystic changes in RCC can be seen in 4%-15%. Only 5% of all lesions are mainly cystic. Those lesions are described by a (modified) Bosniak classification^[130,131] for CECT and remain a challenge for all imaging methods. MRI often gives a higher stage than CECT by depicting more septa and more wall thickening but is less sensitive for calcification^[132]. In the literature the role of calcification in cystic lesions is controversial^[133].

The original classification of Bosniak defines cysts as follows: Bosniak I : hairline thin cyst wall, no calcifications, no solid components; no contrast enhancement; Bosniak II : few hairline thin septae, fine calcification in the wall or in the septae; Bosniak II F: multiple hairline thin septae, minimal smooth thickening of walls or septae, thick or nodular calcification of the wall or septae without contrast enhancement; Bosniak III: thickened irregular or smooth walls or septae with measurable enhancement; Bosniak IV: enhanced soft tissue components independent of the wall or septae (Figure 5).

The classification is used to estimate the chance for

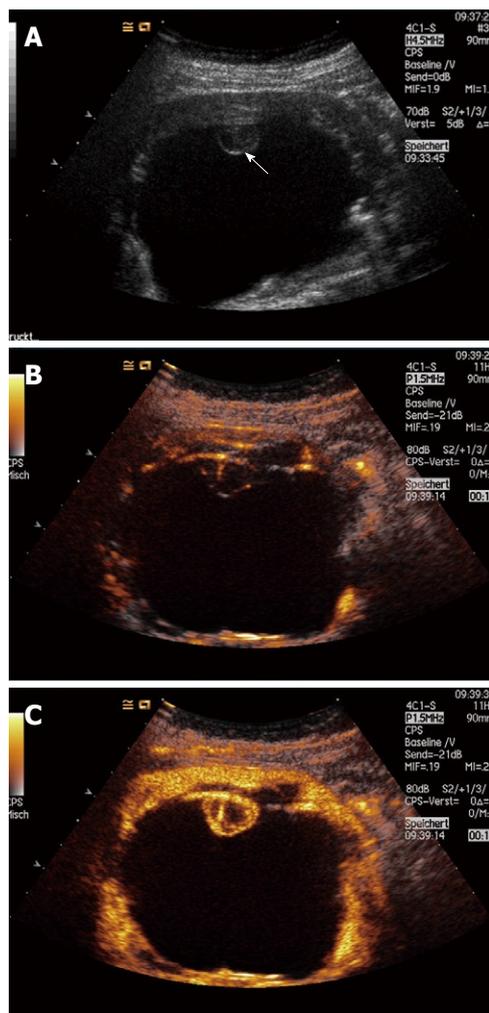


Figure 5 Cystic renal lesion with a small RCC (12 mm × 10 mm) not recognized by CT which has been histologically proven by surgery. B-mode US showed a nodularity inside the cyst (A); CEUS revealed contrast enhancement of the small lesion (B, C)^[134].

malignancy in cystic lesions, but in the group of Bosniak III and IV lesions there are several neoplastic and not necessarily malignant subtypes: cystic (typically clear cell) RCC, multilocular cystic RCC, cystic nephroma, mixed epithelial and stromal tumor. Bosniak I and II do not require further follow-up investigations. Category Bosniak II F has been introduced for lesions which are difficult to define into II or III. Bosniak III lesions are typically considered to require surgery since in the literature a rate of up to 60% malignant lesions is reported^[135]. Bosniak IV lesions are reported to have a risk for malignancy between 67% and 100%^[136,137]. Nevertheless, there is a significant interobserver variability for CECT investigations of cystic masses with complete agreement in only 59% of cases^[138]. Hirai *et al.*^[139] investigated 10 patients with multilocular cystic lesions using conventional CDUS. Histological results were 3/10 (30%) cystic RCC, 3/10 (30%) hemorrhagic renal cysts, 1/10 (10%) benign multilocular cystic nephroma, 2/10 (20%) infected renal cysts and 1/10 (10%) multilocular cyst in a patient with von Hippel-Lindau disease. The authors report on dem-

onstration of pulsatile high resistance flow in the patient with the cystic RCC. In the other lesions flow could only be detected in the peripheral margin where flow was comparable to the flow in the interlobar arteries^[139]. Park *et al.*^[140] compared 31 pathologically confirmed cystic renal masses with SHU 508A and high MI contrast specific imaging and compared the findings with CECT. The diagnostic accuracy for CECT and CEUS for malignancy was 74% and 90%, respectively. There was an agreement in Bosniak's classification for both methods in 74%, in the remaining 26% there was always an upgrade with CEUS (Bosniak I → Bosniak IV in 1/31 patients (3%), Bosniak II → Bosniak IV in 2/31 patients (7%), Bosniak II F → Bosniak III in 2/31 patients (7%), Bosniak III → Bosniak IV in 3/31 patients (10%). In conclusion, 10% of 31 lesions were categorized from Bosniak I or II to IV which leads to therapeutic consequences. Quiaia *et al.*^[141] investigated a series of 40 patients with cystic renal masses with contrast specific software and BR1 and compared the findings with CECT. Three blinded readers in an offsite setting differentiated the lesions according to the Bosniak classification. There were 21/40 (53%) cystic RCC, 2/40 (5%) cystic nephroma (benign), 9/40 (23%) inflammatory or hemorrhagic cysts and 8/40 (20%) uncomplicated cysts. CEUS had a significantly higher diagnostic accuracy than CECT in the detection of malignancy in cystic renal lesions (80%-83% and 63%-75%, respectively)^[141]. Clevvert *et al.*^[142] investigated 32 consecutive patients with 37 complex cystic masses with CEUS with BR1 in comparison to multislice CT. In 14/32 (44%) lesions were surgically resected, the others were followed up for a period of 3 mo to 2 years. In addition, there was a blind reading of video clips of the CEUS investigation. Lesions were categorized as Bosniak II with CECT and CEUS in 15/37 (41%) and in 8/37 (22%) cases, as Bosniak II F in 7/37 (19%) and in 12/37 (32%) cases, as Bosniak III in 8/37 (22%) and in 8/37 (22%) cases, and as Bosniak IV in 7/37 (19%) and in 9/37 (24) cases. CEUS proved to show more septa than CECT and upgraded wall thickness resulting in correction of Bosniak category II to II F. Two masses could not be classified with CECT, were categorized as Bosniak IV using CEUS and proved to be malignant. The authors conclude that CEUS is an additional examination to CECT and can give additional information^[142].

CEUS is currently the best indication for cystic renal lesions in the kidney. There is evidence showing better results in the characterization of cystic renal lesions with therapeutic consequences in more than 10%.

CONCLUSION

CEUS represents the imaging method currently with the highest spatial contrast resolution as well as the highest differentiation between contrast and tissue signal (Figure 4). Its disadvantages are a high observer dependency and often a lack of representative image or video presentation during radiological demonstrations. US and

CEUS are widely used, and sophisticated techniques (hardware and software) improve the diagnostic impact. There is significant evidence for its strength in the detection and characterization of liver lesions, with lesser strength for solid pancreatic lesions. In other indications the evidence is less clear but promising, e.g. splenic and adrenal tumors^[95,96,143,144]. Regarding CEUS for tumor evaluation of the kidneys, the number of published studies is impressive but the conclusive evidence is low.

The majority of tumors of the kidney are RCC. RCC are hypervascular in CEUS in most cases, especially in the case of clear cell histology. Here more than 90% are hypervascular in comparison to the surrounding renal parenchyma. Nevertheless it has to be taken into account that the bigger the lesion the higher the chance for large areas of necrosis or hemorrhage. In current studies with the development of sophisticated US techniques [e.g. cadence pulse sequencing (CPS)], avascular areas could be defined as necrosis by histological investigation^[78,79] (own unpublished data). Avascular areas appear more frequent in large lesions. As those findings were formerly mixed with heterogeneous enhancement patterns the positive and negative predictive value of this sign has not been investigated so far. Papillary RCC in contrast to clear cell RCC was described as hypovascular in one third of cases^[80] but, as papillary RCC are malignant tumors, this finding does not play an important role in clinical practice.

In the staging of malignant tumors of the kidney, the impact of CDUS and CEUS is high. Lymph node metastases, renal vein involvement as well as intraabdominal metastases elsewhere can be detected with results comparable to CECT, although multicenter studies with large patient numbers are not available so far. The detection of the pseudocapsule as a sign of early stage RCC is possible; nevertheless this feature has not been included in the current TNM classification.

The results for CEUS concerning the late phase are not satisfying. CEUS patterns for RCC as well as for benign lesions are heterogeneous for the same tumor entity as well as dissimilar in different studies^[60,93]. Since in the kidney there is no dual blood supply the late phase in the renal parenchyma itself is less pronounced as compared to the liver. In this context, observations in the late phase are limited by certain bubble destruction leading to different results in hyper- and hypoenhancing lesions using different techniques. Nevertheless the late phase is of significant interest but should be investigated with objective measurements using time intensity curves and intermittent imaging to avoid bubble destruction.

Typical AML can be diagnosed with unenhanced CECT if they show a significant fat component. The frequency of atypical AML in CECT is controversial, and depends on necrosis, presence of shunts, low fat content and others. Nevertheless as well as in CECT, in CEUS the contrast agent enhancement patterns do not allow discrimination from RCC in all cases, and in case reports nearly all other tumor entities can present with fatty components as well. The typical AML in CEUS shows less

contrast enhancement in the arterial phase in comparison to the typical clear cell RCC.

Oncocytoma represent a challenge for each imaging method. The typical central stellate scar can be histologically found in about 1/3 of oncocytoma, therefore, imaging methods cannot be sensitive and reliable. Furthermore this sign cannot be differentiated from small necrotic areas in RCC which are seen in a significant proportion of RCC (50%-80%, depending on the size).

Metanephric adenoma is a rare entity and its features in CEUS need to be investigated by a multicenter approach. Up to now there has been no possibility for sharp discrimination with other tumor entities. (1) In the currently available literature, CEUS showed comparable results to CECT in the staging of RCC; (2) The characterization of cystic lesions (this is to date the most promising issue); (3) The detection of blood flow in small masses (differential diagnosis to atypical cysts with elevated density due to protein/blood content on CT); and (4) After local ablative tumor therapy (radiofrequency ablation, cryotherapy).

Possible indications with potential for further investigations are: (1) Differentiation of abscess/infarction *vs* hypovascular tumors because of sharp discrimination of flow *vs* no flow; (2) Follow-up for palliative antiangiogenic therapy in metastatic or recurrent RCC.

Issues to be investigated further for CEUS are as follows: (1) The potential of CEUS to discriminate features for preoperative biopsy, e.g. hypoenhancing lesions < 4 cm; (2) Time-intensity curves, e.g. for oncocytoma and AML; and (3) The rate of benign lesions in the subgroup of small (< 4 cm) hypoenhancing lesions.

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