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Contrast-enhanced ultrasound: The evolving applications

Hui-Xiong Xu

Hui-Xiong Xu, Department of Medical Ultrasonics, The First Affiliated Hospital, Sun Yat-Sen University, The Center of Guangdong Province for the Study of Diagnostic Ultrasound and Interventional Therapy, 58 Zhongshan Road 2, Guangzhou 510080, Guangdong Province, China
Correspondence to: Hui-Xiong Xu, MD, PhD, Professor, Department of Medical Ultrasonics, The First Affiliated Hospital, Sun Yat-Sen University, The Center of Guangdong Province for the Study of Diagnostic Ultrasound and Interventional Therapy, 58 Zhongshan Road 2, Guangzhou 510080, Guangdong Province, China. xuhuixiong@hotmail.com
Telephone: +86-20-87765183 Fax: +86-20-87765183

Abstract

Contrast-enhanced ultrasound (CEUS) is a major breakthrough for ultrasound imaging in recent years. By using a microbubble contrast agent and contrast-specific imaging software, CEUS is able to depict the micro- and macro-circulation of the targeted organ, which in turn leads to improved performance in diagnosis. Due to the special dual blood supply system in the liver, CEUS is particularly suitable for liver imaging. It is evident that CEUS facilitates improvement for characterization of focal liver lesions (FLLs), detection of liver malignancy, guidance for interventional procedures, and evaluation of treatment response after local therapies. CEUS has been demonstrated to be equal to contrast-enhanced computed tomography or magnetic resonance imaging for the characterization of FLLs. In addition, the applicability of CEUS has expanded to non-liver structures such as gallbladder, bile duct, pancreas, kidney, spleen, breast, thyroid, and prostate. The usefulness of CEUS in these applications is confirmed by extensive literature production. Novel applications include detecting bleeding sites and hematomas in patients with abdominal trauma, guiding percutaneous injection therapy and therefore achieving the goal of using interventional ultrasonography in managing splenic trauma, assessing the activity of Crohn's disease, and detecting suspected endoleaks after endovascular abdominal aneurysm repair. Contrast-enhanced intraoperative ultrasound (US) and intracavitary use of CEUS have been developed and clinically studied. The potential use of CEUS involves sentinel lymph node detection, drug or gene delivery, and molecular imaging. In conclusion, the advent of CEUS has greatly enhanced the usefulness of US and even changed the status of US in clinical practice. The application of CEUS in the clinic is continuously evolving and it is expected that its use will be expanded further in the future.

INTRODUCTION

Ultrasound (US) is one of the most widely used imaging

modalities in the clinic, largely owing to its characteristics such as real-time scanning, no radiation, easy performance, and cost-effectiveness. With the improvement of related technologies, US not only provides high-resolution sectional anatomic images, but also provides detailed blood flow information within the region of interest (ROI), which leads to wide applicability of US in various fields. However, when compared with other tomographic modalities such as computed tomography (CT) or magnetic resonance imaging (MRI), conventional US has been generally regarded to be inferior since it has low ability to depict the microcirculation within the ROI. This is especially true for tumor imaging because the information on microcirculation is essential for imaging diagnosis. Therefore, in the clinic, most patients have to be referred to CT or MRI examination for further confirmation.

The beginning of the new millennium has witnessed a revolutionary evolution of US. Contrast-enhanced US (CEUS), which not only improves the diagnostic performance in numerous pathological conditions, but has also, changed the status of US in some fields. CEUS consists of two basic elements, one is the ultrasound contrast agent (UCA), and the other is contrast-specific imaging technique. The first generation of UCAs such as agitated saline, hydrogen peroxide, air, and carbon dioxide can not pass through the pulmonary circulation, thus only achieve right heart imaging. The second generation of UCAs is stabilized with different substances, the surface of which is made of phospholipid, albumin, or polymers. The mean diameter of the second generation of UCAs is less than 8 μm which guarantees that the UCA can pass through the pulmonary circulation and reach various organs. Second generation UCAs also have prolonged longevity due to their lower solubility in water and have a strong harmonic response.

An UCA in the circulation interacts with the US beam depending on the energy of insonation. At low acoustic powers (low mechanical index), the bubbles reflect US and increase the echoes. As the acoustic power increases, the bubbles develop nonlinear resonance, resulting in the generation of harmonic signals. At higher powers, bubble destruction occurs, producing a strong but transient effect that may be seen as an intense signal. Most of the contrast specific techniques such as pulse and phase inversion discriminate between the nonlinear harmonic response from microbubbles and the response from tissue, thus allowing detection of the signal of microbubbles in a gray-scale image. High MI technologies allow intermittent scanning of the lesion during the various phases of contrast enhancement. Conversely, the contrast-specific imaging technique operates under low MI (i.e. less than 0.2), thus the UCA in the acoustic field would not be destroyed and the scanning fashion is continuous. These nondestructive techniques require administration of second-generation UCAs which are able to reflect the US beam at low acoustic power.

In the CEUS procedure, firstly the UCA is administered through the peripheral veins, and then the ROI is exposed to an acoustic field. When the UCA microbubbles arrive in the ROI, the UCA in the micro- and macro-circulation will interact with the acoustic wave and nonlinear signals will be generated, whereas no or few nonlinear signals are generated from the tissues. Thus an improved signal-to-noise ratio is achieved, and UCA can be used as a tracer to depict the micro- and macro-circulation[1,2].

CEUS FOR LIVER USE

CEUS is particularly suitable for liver imaging, which is largely due to the fact that the liver has a dual blood supply system[3]. The UCAs in the hepatic artery are firstly visualized, followed by those in the portal vein. Hence, the CEUS process is always divided into the arterial phase (< 30 s from the injection of UCA), portal phase (31-121 s), and late phase (> 120 s). The enhancement extent of lesions is divided into hyper-, iso-, hypo-, and non-enhancement compared with the adjacent liver tissue[4].

Characterization

On CEUS, hyperenhancement in the arterial phase and subsequent washout to hypoenhancement often indicates malignancy, and sustained enhancement in the portal or late phase always indicates benignity. This algorithm has been endorsed by the 2008 European Guideline for CEUS[4]. Xu et al[5] compared the diagnostic capability of CEUS with baseline US (BUS) in 200 patients with small focal liver lesions (FLLs) (equal or less than 3 cm). The sensitivity, negative predictive value, and accuracy of BUS and CEUS in differentiating between malignant and benign FLLs were 59.6%-71.1% vs 89.5%-93.9%, 63.2%-69.2% vs 87.4%-91.8% and 73.5%-77.5% vs 92.5%, respectively (all $P < 0.001$). A better interobserver agreement was achieved using CEUS (κ = 0.425 with BUS vs κ = 0.716 with CEUS). Similar results were found by other investigators[6,7].

Besides making the distinction between malignancy and benignity, many FLLs have special enhancement patterns on CEUS, which allow precise lesion type diagnosis for most FLLs. For example, homogeneous or heterogeneous hyperenhancement during the arterial phase and washout in late phase are clues for hepatocellular carcinoma (HCC), and peripheral rim-like hyperenhancement and subsequent washout (or even a "black hole" sign) often indicates metastatic liver cancer. The typical findings of hemangioma in CEUS are peripheral nodular hyperenhancement, centripetal fill in, and sustained enhancement in late phase. The sensitivity and specificity are as high as 96% and 98%, respectively in diagnosing hemangioma. The findings

of focal nodular hyperplasia, the second most common FLL, in CEUS are rapid arterial hyperenhancement with centrifugal radiating or "spoke-wheel" pattern, and sustained hyper- or iso-enhancement in late phase. These specific findings on CEUS greatly improved the ability to determine the nature of the lesions. This is especially clinically relevant in benign lesions or incidental lesions as more expensive examinations such as CT or MRI can be avoided[4-15].

CEUS has the potential to differentiate some FLLs such as HCC. It was suggested that well-differentiated HCC tends to show isoenhancement during portal or late phase and moderately- or poorly-differentiated HCC tends to show hypoenhancement. The former also washes out more quickly in enhancement extent in comparison with the latter on CEUS[16]. CEUS may also be used to evaluate the multi-step carcinogenesis of HCC by evaluating the change in intranodular hemodynamics, which is helpful in detecting premalignant lesions or HCC at an early stage[17]. When compared with CT or MRI, many studies have proven that CEUS is able to achieve the same or even higher characterization of FLLs [18]. This is reasonable when considering that CEUS can document the continuous change in intralesional hemodynamics and UCA is a real blood pool agent so that it is suitable for depicting the microcirculation that is essential for diagnosis.

Detection
Conventional US is less accurate in detecting and staging FLLs than CT, MRI, and intraoperative US. The main reasons for this are that conventional US has decreased ability to visualize small lesions (often less than 1 cm), isoechoic lesions (generally found in small lesions), lesions in coarse livers and lesions located in difficult anatomic areas (e.g. near the diaphragmatic dome).

Most malignant FLLs show hypoenhancement in portal or late phase, which facilitates the detection of small lesions since sufficient contrast between the lesion and the liver is achieved. As a result, many publications have proven that CEUS improves the detection of small lesions with conventional US, and some studies even suggest CEUS is superior to CT in the detection of small lesions[19,20]. When considering the balance between lesion size and location, the overall performance in detection for both CEUS and CT is comparable. The use of the newly launched UCA, Sonazoid further increases the ability of CEUS in FLL detection. Sonazoid allows vascular imaging and Kupffer imaging, and is extremely stable and tolerable for multiple scanning at least up to 60 min in the post-vascular phase, and may further improve the detection rate of HCC with CEUS[21]. CEUS with Sonazoid detected liver malignancy as defects on the sinusoidal phase with a high sensitivity of 95%, specificity of 93%, positive predictive value of 99%, and negative predictive value of 97%. The improved performance makes CEUS a suitable modality

for surveillance in patients at high risk for HCC, patients with previous known malignancy, or patients in follow-up after treatment for cancer.

Guidance
Conventional US is the most widely used modality for guidance of tumor biopsy or ablation therapy. However, its role is limited when the target lesion is isoechoic or when the lesion shows infiltrative character and has no definite margin. In patients with liver cancer who have residual tumor after ablation therapy or transarterial chemoembolization (TACE), conventional US has low ability to detect viable tumor when a repeat ablation therapy is scheduled. Under such circumstances, CEUS can be applied for guidance. CEUS may detect more small foci which are invisible on conventional US or CT, thus is useful for patient selection before ablation therapy. CEUS can determine the tumor size and margin more accurately, which might be larger than that depicted by conventional US. Thus, it is helpful for treatment planning or even for excluding some patients not suitable for ablation. Under CEUS guidance, the residual tumor can be well delineated and targeted by recognizing the hyperenhancing area within or adjacent to the treatment zone during the arterial phase or hypoenhancing area during late phase[22].

Treatment response evaluation
Local treatment therapies, mainly TACE and ablation, have been accepted as curative options for early HCC. Recently, anti-angiogenesis methods have also been introduced into the clinic to treat advanced HCC. In these therapies, the tumor is not eradicated, but is devascularized or coagulated. Therefore, it is of paramount importance to evaluate the local treatment response and detect possible viable tumor. Previously, contrast-enhanced CT or MRI has been regarded as the gold standard for treatment response evaluation. Recently, a prospective multi-center study in China has proven that CEUS has the same ability to evaluate treatment response as CT or MRI, thus CEUS can be used as an alternative to CT or MRI for this purpose[23].

Liver CEUS improves depiction of intralesional vascularity and perfusion in FLLs, which always leads to a high contrast between the lesion and the surrounding tissue, especially when the lesion is hypervascular or hypovascular or when the lesion shows washout in late phase, thus it is suitable for three-dimensional US (3DUS). Three-dimensional CEUS (3D-CEUS) combines the advantages of 3DUS and CEUS[24]. Xu et al[25] investigated the potential usefulness of 3D-CEUS in evaluating the treatment response in liver cancer after local therapies. 3D-CEUS did not change the diagnosis in any patient compared with 2D-CEUS. However, 3D-CEUS changed the management in 2.8% of lesions, increased confidence but made no change in diagnosis in 79.5% of lesions, added some information but did not change management

or diagnosis in 14.0%, and made no change in 3.7%, respectively. The authors concluded that 3D-CEUS enhanced the diagnostic confidence in the majority of the patients and even changed the management in some patients. 3D-CEUS has potential usefulness in evaluating treatment response in liver cancer after local therapies.

The role of CEUS in evaluating tumor response to anti-angiogenic therapies has promising potential. Clinical trials have shown that CEUS can be used to assess the anticancer efficacy of anti-angiogenic treatment, for which conventional efficacy criteria based on tumor size measurement are unsuitable. Reduction in tumor vascularization can easily be detected in responders after 1-2 wk and is correlated with progression-free survival and overall survival. More sophisticated methods use quantitative approaches to measure the amount and the time course of bolus or reperfusion curves and have shown great promise in revealing effective tumor response to anti-angiogenic drugs in humans before tumor shrinkage occurs[26-28].

CEUS FOR NON-LIVER USE

The advent of CEUS not only enhances the use of US in the liver for tumor diagnosis, guidance and follow-up[29-31], but also provides solutions in many non-liver organs, including the gallbladder, bile duct, pancreas, and kidney.

Gallbladder
Conventional US is the first-line imaging investigation for the diagnosis of gallbladder diseases, but has difficulty in determining the nature of the gallbladder lesions in some cases, especially in differentiating chronic chole-cystitis with thickened wall from gallbladder carcinoma with thickened wall or differentiating motionless sludge from gallbladder cancer. Xie et al[32] found that hyperenhancement or isoenhancement in the early phase and then fading out to hypoenhancement within 35 s after contrast agent administration was found in 90.9% of carcinomas and 17.0% of benign lesions. Destruction of the intactness of the gallbladder wall, that was, the internal or the outer wall of the gallbladder was discontinuous on CEUS, and was not found in benign diseases, but was present in 84.8% of carcinomas. They summarized that washout of contrast agent within 35 s after injection and destruction of gallbladder wall intactness on CEUS is highly suggestive of gallbladder malignancy. CEUS is particularly useful in differentiating gallbladder carcinomas and motionless biliary sludge or chronic cholecystitis with thickened gallbladder wall.

Bile duct
The use of CEUS has extended to the bile duct in recent years and promising results have been achieved. CEUS is especially useful in the diagnosis of malignancy of the bile duct, including intrahepatic, hilar, and extrahepatic

bile ducts. Intrahepatic cholangiocarcinoma (ICC) is a malignant epithelial tumor that originates at the second branch (segmental branch) or the proximal branch of the intrahepatic bile ducts and is the second most common primary malignant tumor in the liver. Xu et al[33] summarized the CEUS findings of ICC, and Chen et al[34] compared the enhancement patterns of ICC between CEUS and contrast-enhanced CT. They found that during the arterial phases, four enhancement patterns were present on CEUS, which were: (1) peripheral irregular rim-like hyperenhancement (47.5%), (2) diffuse heterogeneous hyperenhancement (22.5%), (3) diffuse homogeneous hyperenhancement (12.5%), and (4) diffuse heterogeneous hypoenhancement (17.5%). When compared with CT, the enhancement patterns of ICC on CEUS were consistent with those on CECT in the arterial phase, whereas in the portal phase, ICC faded out more obviously on CEUS than on CECT. CEUS had the same accuracy as CECT in diagnosing ICCs, and so can be used as a new modality for the characterization of ICC. Although BUS has a low ability in differentiating ICC and HCC, Chen et al[35] found that CEUS greatly improved the diagnostic performance in this respect.

The primary investigation for suspected hilar bile duct cancer (i.e. Klatskin tumor) is a transabdominal US examination, which is highly sensitive for confirming biliary duct dilatation, localizing the site of obstruction and excluding gallstones. However, it has a limited role in determining the nature of the obstruction and defining the extent of tumor involvement since the lesion is always isoechoic to surrounding liver and the infiltrative nature of the lesion. Xu et al[36] compared the enhancement pattern of Klatskin tumor between CEUS and CECT. They found that the enhancement pattern of hilar cholangiocarcinoma on CEUS was similar to that on CECT in the arterial phase, whereas in the portal phase, hilar cholangiocarcinoma is more likely to show hypoenhancement on CEUS. CEUS and CECT lead to similar results in the evaluation of portal vein infiltration and the diagnosis of this entity. Therefore, CEUS has potential as a tool for the characterization of Klatskin tumors.

The use of CEUS in the extrahepatic bile duct has also been explored. Xu et al[37] reported a case of villous adenoma in the extrahepatic bile duct that was successfully diagnosed with CEUS. However, more data are needed on the use of CEUS in this aspect. Theoretically, CEUS may be valuable in distinguishing between tumor and debris or stone without obvious acoustic shadowing.

Pancreas
The study of the pancreas is a new and promising application of CEUS. CEUS can be used to improve delineation of pancreatic lesions compared with conventional US, and to characterize lesions already visible on US. Ductal adenocarcinoma is the most frequent malignancy

in the pancreas. At CEUS, adenocarcinomas are often hypovascularized as compared to the surrounding tissue. Focal pancreatitis has been reported to have similar enhancement extent and pattern with the surrounding pancreas. Contrast quantification software supplements a subjective visual assessment with objective criteria to facilitate the differential diagnosis of focal lesions in pancreatic cancer and chronic pancreatitis[38]. On the other hand, neuroendocrine tumors are hypervascularized lesions. Masses associated with pancreatitis have a different vascularization pattern depending on the degree of inflammation and necrosis. Cystadenomas frequently show many vessels along fibrotic strands. Pseudocysts, the most common cystic lesions of the pancreas, are non-vascularized[39,40]. In the recently launched guideline and good clinical practice recommendation for CEUS, CEUS of the pancreas has been recommended in the following indications: exact dimension depiction and margin depiction of pancreatic lesions and their relationship with adjacent vessels; characterization of focal pancreatic lesions (especially ductal adenocarcinoma, neuroendocrine tumor and focal pancreatitis); differential diagnosis between pseudo cysts and cystic pancreatic tumors; and differentiation of the vascular (solid) or avascular (liquid/necrotic) components of the lesion[4]. CEUS may also be useful in determining treatment efficacy and outcome after chemotherapy[41].

Kidney
Conventional US has been widely used in many centers as the first promising imaging modality for measuring the size of the kidney, confirming or ruling out focal lesions, depicting blood flow perfusion, evaluating the status of transplanted kidneys, and even detecting renal artery stenosis. However, the acoustic properties of conventional US are sometimes not enough to make a distinction between benign and malignant lesions or to evaluate blood flow perfusion. Therefore, significant attention has been paid to CEUS of the kidney[42]. Up to now there have been no reported side effects of contrast agent in the kidney; therefore CEUS is applicable in patients with impaired kidney function or ureteric obstruction which may be contraindications for contrast-enhanced CT or MRI.

CEUS is valuable in distinguishing pseudotumors due to developmental anomaly and neoplasm. The former shows isoenhancement during all phases in relation to the surrounding parenchyma, whereas the latter may show different enhancement patterns compared with normal tissue. The role of CEUS in the characterization of focal renal lesions is equivocal. Some authors think there are no reliable criteria to differentiate benign and malignant focal renal lesions, whereas other authors have the opposite opinion. Xu et al[43] believed that hyper- or iso-enhancement during the early phase, subsequent washout in late phase, inhomogeneous enhancement, and perilesional rim-like enhancement are clues for renal

cell carcinomas (RCCs), which might be useful for the characterization of RCCs. Complex cysts of the kidney, which are characterized by a thickened or irregular wall, calcifications, septa or solid components, especially those classified as type 2F, 3 or 4 according to the Bosniak classification, are probably the best indication for renal CEUS. CEUS helps to depict blood flow perfusion within the wall, septa and solid components, thus is useful for the characterization of lesions in which CT or MRI studies are inconclusive or contraindicated[4].

CEUS is also valuable in evaluating complications after kidney transplantation. CEUS may help to diagnose vascular stenosis or thrombosis, focal infarction, shunts and hematomas with great confidence. CEUS is also useful in evaluating microvascular renal allograft perfusion[44].

Spleen
CEUS has been used for the characterization of focal splenic lesions. On CEUS, benign lesions appeared predominately non- or isoenhancing relative to splenic parenchyma. The combination of contrast enhancement in the early phase followed by rapid wash-out and demarcation of the lesion without contrast enhancement in the parenchymal phase (60 s after injection) was typical for malignant lesions[45]. For correct diagnosis of benignancy or malignancy, the overall accuracy was 43%-74% before CEUS *vs* 81%-92% after CEUS[46]. CEUS improves the characterization of focal splenic lesions with and without the availability of clinical data.

Breast
US has played a key role in the evaluation of breast lesions in clinical settings. Liu et al[47] evaluated the usefulness of CEUS using the microvascular imaging technique in the diagnosis of breast lesions. The authors found that non-enhancement was suggestive of benignity, with a sensitivity of 18.3%, specificity of 97.7%, positive predictive value of 91.7%, negative predictive value of 46.2%, and accuracy of 51.5%. The peripheral enhancement pattern was suggestive of malignancy, with a sensitivity of 39.5%, specificity of 98.3%, positive predictive value of 94.4%, negative predictive value of 69.4%, and accuracy of 73.8%. An accurate assessment of tumor size is necessary when selecting patients for breast-conserving surgery. Underestimation of tumor size may result in incomplete excisions, leading to re-excisions or higher local recurrence rates. Jiang et al[48] found that tumor size increase on CEUS compared with conventional US existed in some breast cancers and analyzed the correlation with pathology. However, it is difficult to predict whether the size of the breast cancer measured increases at CEUS based on the margin characteristics shown on conventional US.

Thyroid
The role of CEUS in the thyroid is controversial.

Carraro et al[49] calculated the percentage of intranodular contrast agent with the use of 3D-CEUS. They confirmed that malignant nodules had a higher internal vasculature (52.3% ± 15.7%) than benign nodules (14.3% ± 5.3%) and believed this methodology could be useful in improving nodule differentiation in thyroid US exams. On the other hand, Bartolotta et al[50] found there was no obvious difference between malignant and benign thyroid nodules and concluded that overlapping findings seem to limit the potential of this technique in the characterization of thyroid nodules.

Prostate
Prostate cancer has increased continuously in recent years. Tang et al[51] assessed the value of contrast-enhanced gray-scale transrectal US (CETRUS) in predicting the nature of peripheral zone hypoechoic lesions of the prostate. They found that malignant hypoechoic nodules in the peripheral zone of the prostate are more likely to enhance early and more intensely on CETRUS. A non-enhanced hypoechoic peripheral zone lesion is more likely to be benign.

NOVEL APPLICATIONS

Blunt abdominal trauma
Since UCA can be used as a tracer of blood flow, CEUS is able to detect bleeding sites and hematomas in patients with abdominal trauma[52]. During 5 years of experience in using CEUS to identify traumatic abdominal lesions, the sensitivity, specificity and positive and negative predictive values of US were 70.2%, 59.2%, 74.7% and 53.7%, respectively, whereas those of CEUS were 96.4%, 98%, 98.8% and 94.1%, respectively. The technique is able to detect active bleeding and vascular lesions, avoids exposure to ionizing radiation and is useful for monitoring patients undergoing conservative treatment[53].

CEUS can also be used to guide percutaneous injection therapy and therefore achieve the goal of using interventional ultrasonography in managing splenic trauma. In a study by Tang et al[54], six patients with grade 3 or 4 splenic injuries as determined by CEUS and CECT were given hemocoagulase atrox and absorbable cyanoacrylate percutaneously, which were injected into the injured region and active bleeding site, respectively, under CEUS guidance. Among the 6 patients, 4 cases of CEUS-guided hemostatic injection were successful without complications. Re-hemorrhage occurred in 1 patient, and a traumatic arteriovenous fistula occurred in the other patient; repeated injection therapy in these 2 patients was effective. During the follow-up, there were no complications, and spleen perfusion recovered gradually.

Crohn's disease
CEUS provides a new method to assess the activity of Crohn's disease[55]. Mural contrast enhancement shown on CEUS in patients with active disease at endoscopy was markedly increased in comparison with enhancement in patients with inactive disease. Multivariate logistic regression analysis revealed that an increase in wall brightness was a significant and independent variable predictive of severity grade at endoscopy. Quantitative measurements of bowel enhancement obtained by using CEUS correlate with severity grade determined at endoscopy. Thus CEUS could be a useful technique to monitor the activity of Crohn's disease[56].

Detecting suspected endoleaks after endovascular abdominal aneurysm repair
CEUS is able to depict endoleaks accurately after endovascular abdominal aneurysm repair and stent-graft procedure in dissected and ulcerated aorta. It seems to be superior in characterizing the type of endoleak and can be established in order to reduce iodized contrast agent and radiation exposure in follow-up. In a series of 30 patients, 21 endoleaks were identified by CT angiography (CTA) and 22 by CEUS. Thus, the sensitivity of CEUS was 99% and its specificity was 85%[57]. In contrast to CTA, CEUS can be offered to patients with chronic renal insufficiency and allows a dynamic examination and a perfusion analysis.

Contrast-enhanced intraoperative US (CE-IOUS)
The clinical value of CE-IOUS as a novel tool in the hepatic staging of patients undergoing liver resection has been assessed. In a series of 60 patients scheduled to undergo liver resection for metastatic disease, 3 patients were excluded due to disseminated disease on exploration by CE-IOUS. CE-IOUS was more sensitive than CT/MR and IOUS in detecting liver metastases (96.1% vs 76.7% and 81.5%, respectively); it altered surgical management in 29.8% of cases due to additional metastases, fewer metastases, benign lesions wrongly diagnosed as metastasis on IOUS/CT, or vascular proximity. CE-IOUS altered combined IOUS/CT/MR staging in 35.1% of cases. These preliminary results suggest that CE-IOUS is an essential tool prior to liver resection for metastases[58].

CE-IOUS was also used in neurosurgery. Malignant brain tumors might not be completely removed in surgery because there is no definite border between the tumor and normal brain tissue. He et al[59] investigated the feasibility and value of CE-IOUS in neurosurgery. Their results showed that the tumor border was more distinguishable from normal brain tissue on CEUS than on conventional US. In addition, intraoperative CEUS could improve the definition of residual tumor during surgery.

Gynecological use
Zhou et al[60] used CEUS to evaluate response to high intensity focused ultrasound ablation of uterine fibroids,

using CEMRI as the standard of reference. The diagnostic accuracy of CEUS was 100%.

Intracavitary use of CEUS

Besides intravascular use, CEUS is increasingly used for intracavitary purposes. CEUS is used for the diagnosis of vesicoureteric reflux after intravesical instillation. It is especially suitable for children since it can reduce possible ionizing radiation in association with voiding cystourethrography[61]. CEUS is also used to evaluate tubal patency in patients with primary or secondary infertility[62].

In percutaneous drainage procedures, CEUS allows visualization of the location of the drainage duct following intraductal injection. Thus CEUS can be used to determine whether the drainage duct position is appropriate or not, obstructed or not, and can even depict the shape of the biliary tree in percutaneous transhepatic cholangial drainage[63]. CEUS is also useful in the diagnosis of biliary leakage following T-tube removal[64].

POTENTIAL USE

Sentinel lymph node (SLN) detection

Lymphosonography, or CEUS-guided SLN detection, as a technique for demonstrating lymphatic drainage, has been introduced in some experimental studies. In this procedure, transcutaneous injection of an UCA is performed and CEUS is used to identify draining lymphatic channels and SLNs. This use of CEUS is technically feasible, as was demonstrated by various studies[65,66].

Drug or gene delivery

The microbubble contrast agent interacts with the acoustic wave in the acoustic field. The contrast agent itself will serve as a cavitation nucleus and lower the threshold level for cavitation[67,68]. In an experimental study, Nie et al[69] found that compared with the group treated by US alone, KDR-tk gene therapy treated by US combined with SonoVue inhibited tumor growth and increased survival time of Hepa1-6 tumor-bearing mice. It was concluded that gene therapy mediated by US exposure enhanced by a microbubble contrast agent may become a new treatment option for HCC. Based on the same principle, UCA was used for drug delivery or in the treatment of acute intravascular thrombi[70,71].

Molecular imaging

Techniques for noninvasive imaging of specific disease-related molecular changes are being developed to enhance diagnosis and therapeutic decision-making. Molecular imaging with CEUS relies on the detection of the acoustic signal produced by microbubble or nanoparticle agents that are targeted to the sites of disease. The potential use of CEUS-based molecular imaging in atherosclerosis, post-ischemic inflammation, angiogenesis, transplant rejection and thrombus formation have been investigated, and is undoubtedly an important development trend[72-76].

CONCLUSION

The role of CEUS in liver imaging is accepted in many clinical settings, such as in the characterization of FLLs, detection of FLLs, treatment response evaluation after local therapy, guidance in interventional procedures for invisible or suboptimal lesions on BUS. Most gallbladder diseases can be correctly diagnosed by conventional US, whereas CEUS is useful in differentiating gallbladder carcinomas and motionless biliary sludge or chronic cholecystitis with thickened gallbladder wall. CEUS also can be used to differentiate between ICC and HCC, and is useful in demarcating Klatskin's tumor. CEUS is useful in the characterization of focal pancreatic lesions, differential diagnosis between pseudo cysts and cystic pancreatic tumors, and differentiation of the vascular (solid) or avascular (liquid/necrotic) components of the lesion. CEUS may also be useful in determining treatment efficacy and outcome after chemotherapy for pancreatic cancer. CEUS is helpful in the characterization of complex cystic lesions and suspected cystic renal carcinoma, and can be used for the evaluation of anatomical variations mimicking renal tumor. CEUS is particularly useful for patients with contraindications for the use of CT or MR contrast agents.

The role of CEUS in other organs such as spleen, breast, and thyroid are still under investigation, and more evidence is needed to validate its usefulness. The novel applications such as use in blunt trauma, Crohn's disease, and gynecology also need further confirmation. The use of CEUS in molecular imaging and in gene therapy still requires further investigation.

In general, the advent of CEUS has greatly enhanced the usefulness of US and even changed the status of US in clinical practice. The application of CEUS in the clinic is continuously evolving and it is expected that its use will be expanded further in the future.

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