

Ultrasound Examination in Detection and Characterization of Colorectal Liver Metastases

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INTRODUCTION

Colorectal cancer (CRC) globally affects over one million people each year and is one of the leading causes of death worldwide^[1]. Mortality of CRC is predominately affected by progression of liver metastases^[2]. Up to 50-70% of the patients may develop colorectal liver metastases (CRLMs) during the course of disease^[3]. Treatment of CRLMs is aimed at resection either primarily or after down staging with chemotherapy. Surgical resection provides the best opportunity for long-term survival and is the only potentially curative treatment for CRLMs in selected groups, the 5-year median survival has been reported up to 58%^[4]. Patients with untreated but potentially resectable metastases show a median survival of 8 months and the 5-year survival rate less than 5%^[5-6]. Eligibility for surgical treatment requires strict criteria. Besides an adequate clinical condition, all liver lesions have to be completely resectable after evaluation. Thus, the detection and characterization of CRLMs is of fundamental importance for achieving cancer control in patients with diagnosed colorectal cancer^[7]. The pre-surgical evaluation of CRLMs relies firstly and almost totally on imaging studies, which could provide information including the exact number, regional distribution, size and the volume of the remaining liver. In patients who are not suitable candidates for resection, chemotherapy alone or in combination with local or regional treatments such as radiofrequency ablation, microwave ablation and transarterial chemotherapy are the option. For these local treatments, imaging also plays an integral role in treatment planning, guidance and evaluation of therapeutic effects^[8].

Noninvasive detection and diagnosis of CRLMs during clinical practice mainly depends on imaging techniques, such as contrast-enhanced computed tomography (CECT), contrast-enhanced magnetic resonance imaging (CEMRI), positron emission tomography-computed tomography (PET-CT), ultrasound (US) and contrast-enhanced ultrasound (CEUS). CECT is the most useful modality for initial staging and post treatment surveillance

ABSTRACT

The detection and characterization of colorectal liver metastases (CRLMs) depend firstly and totally on imaging studies. Transabdominal ultrasound (US) is the most cost-effective and readily available modality to screen the liver. Contrast-enhanced ultrasound (CEUS) has shown high performance comparable to contrast-enhanced computed tomography and magnetic resonance imaging in detection and characterization of CRLMs. Intraoperative ultrasonography (IOUS) is the golden standard for detection of CRLMs and frequently used for intraoperative decision making. This review illustrates the findings on ultrasonic examinations (including US, CEUS and IOUS) of CRLMs with an emphasis on unique capability and appropriate indications of ultrasonic examinations in the detection and characterization of CRLMs. We aim to highlight the advantages of ultrasonic examinations, as well as underscoring potential pitfalls and limitations.

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of metastasis for colorectal cancer patients, which sensitivity in detection of liver metastases ranged from 68% to 85%^[9-11]. CRLMs are typically hypo attenuating lesions compared with the surrounding liver parenchyma on plain scan and easily identified on portal phase of dynamic CECT scan^[12]. However, for CRLMs with diameter smaller than 1cm, those after chemotherapy and those in diffuse liver disease such as fatty liver, confident detection and characterization usually remain practical limitations of CECT^[13-18]. CEMRI is considered superior to CECT and PET-CT in the detection and characterization of small liver lesions, especially in the presence of background fatty liver or post chemotherapy^[19-20]. CEMRI shows higher sensitivity than CECT in detection of CRLM, ranged from 70% to 98%^[20-21]. During the hepatobiliary phase, liver parenchyma shows high signal on T1-weighted MRI (gadoteric-enhanced dynamic MRI), whereas metastatic lesions maintain their native dark signal^[22]. PET-CT has a problem-solving role in the detection of distant metastasis and in post treatment evaluation^[23]. However, CECT, CEMRI and PET-CT are less cost-effective for repeated evaluations during the long term followup compared with US. And some patients may not suitable for the radiological imaging studies in case of hypersensitivity to iodinated contrast media, heart or kidney failure, implantation of pacemakers and claustrophobia, and so on^[24].

Trans abdominal US is the most cost-effective and readily available modality to screen the liver, but it shows low sensitivity for the detection of metastatic lesions and may fail to recognize over 50% of liver metastases^[25]. In contrast, intraoperative ultrasonography (IOUS) provides high-resolution imaging and is frequently used for intraoperative decision making. The reported sensitivity of IOUS ranged from 85% to 95%^[26-27]. However, the performance of US and IOUS are dependent on the operator's experience, lesion size, location, and echogenicity of the lesions. CEUS using the second generation microbubble contrast agents may provide a safe and effective way to depict the vascularity of the target tissue. CEUS has been widely used in many different applications, especially in the detection and diagnosis of FLLs^[28]. In many clinical trials, CEUS has shown high performance comparable to CECT and CEMRI in detection and characterization of FLLs^[29-31]. Malignant FLLs, especially liver metastasis usually present arterial rim-like or homogeneous hyper-enhancement with "defect of enhancement" during the late phase or liver specific phase of CEUS, which makes the characterization and detection as accurate and easy as CECT^[32]. A systematic review and cost-effectiveness analysis^[24] indicated that CEUS using SonoVue[®] could not only provide similar diagnostic performance with CECT and CEMRI in assessment of FLLs, but also be most cost-effective, especially in the surveillance of cirrhosis patients and characterization of incidentally detected FLLs.

This article illustrates the findings on ultrasonic examinations (including US, CEUS, IOUS and IO-CEUS) of CRLMs with an emphasis on unique capability and appropriate indications of ultrasonic examinations in the detection and characterization of CRLMs. We aim to highlight the advantages of ultrasonic examinations, as well as underscoring potential pitfalls and limitations.

US

With the advantages of cost-effective and ease of use, US used to be the first choice for evaluation of liver disease. The sensitivity of US in detection of CRLMs is low and variable, ranging from 50% to 76% as reported in the literature^[7,33]. The sensitivity mainly depends on the size of CRLMs, and only 20% for lesions smaller

than 10 mm in diameter^[34]. The efficiency of US scan is dependent on both the operator and the patient, where the operator's expertise and the patient's habitus (fat and body mass index) and intestinal gas may variably influence the results of US evaluation. However, the major limit of US is relatively low contrast between lesions and the liver parenchyma. In particular, iso-echoic metastases are generally difficult to be detected as they present similar acoustic impedance to the surrounding parenchyma^[35]. Liver steatosis, a common occurrence in patients receiving chemotherapy, is also an impediment to US performance for lesion detection^[36]. Bipat *et al.*^[37] recommended that US should only be used to distinguish patients with diffuse CRLMs who are no longer eligible for curative treatment, from those with few metastases or other liver lesions requiring further imaging evaluation.

The US appearance of CRLMs is variable. Typical US findings of CRLMs are multiple hypo-echoic nodules in liver, surrounded by the halo sign, which called "bull's-eye" sign (Figure 1) or "concentric circles" sign. However, only a few lesions may show the typical appearance. Inadequate lesion characterization is a challenging with US. For example, hyper-echoic CRLMs are usually difficult to differentiate from hemangiomas.

According to our experiences, the performance of US in detection and characterization of CRLMs, especially for those smaller than 10mm in diameter, could be significantly improved by combining high-frequency linear probe and routine convex probe during the evaluation. High-frequency linear probe could help to detect more tiny CRLMs and present clear boundary and halo sign when the lesions located within 60mm below the liver capsule. And by combining the findings of convex and linear probe together, the sensitivity of US in detection CRLMs might be improved to 85%.

CEUS

Appropriate indications

CEUS has already achieved an established role in the diagnosis and detection of FLLs in clinical practice^[30,38-41]. According to the guidelines of World Federation for Ultrasound in Medicine and Biology (WFUMB) and European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB)^[28], CEUS is recommended for the following indications:

- (1) To characterize all nodules found on surveillance and routine US.
- (2) To characterize indeterminate (usually small) lesions shown on either CECT or CEMRI.
- (3) Surveillance of oncology patients where CEUS has been useful previously. Recommended to replace unenhanced US with CEUS for the evaluation of CRLMs after chemotherapy^[42].



Figure 1 A 60-year-old male patient with colon cancer. US showed multiple nodules (red asterisk) in the liver surrounded by halo sign, which called "bull's-eye" sign.

(4) To contribute to the selection of nodule(s) for biopsy when they are multiple or have different contrast patterns.

(5) For treatment planning in selected cases to assess the number and location of liver metastases, either alone or as complementary to CECT and/or CEMRI.

Contrast agent

The basic principles of CEUS are cancellation and/or separation of linear US signals from tissue and utilization of the nonlinear response from ultrasound contrast agent (UCA) microbubbles^[28]. The currently used UCA are microbubbles consisting of gas bubbles stabilized by a shell^[28]. For CEUS used in liver examinations, SonoVue® (BR1; Bracco, Milan, Italy) and Sonazoid® (GE Healthcare, Oslo, Norway) are the most popular UCA in clinical practice. SonoVue® is a sulphur hexafluoride (SF₆) microbubble which acts as a real blood pool contrast agent and allows real time imaging. Sonazoid® is a perflubutane (C₄F₁₀) microbubble stabilized with phospholipid shells which could not only act as a blood tracer but also as reticuloendothelial system specific UCA^[43]. According to the guidelines of WFUMB and EFSUMB^[28], enhancement pattern of focal liver lesions (FLLs) should be described separately for the different phases, which comprise the arterial phase (starts at 10-20s and end at 30-45s after injection), the portal venous phase (starts at 30-45s and end at 120s after injection), the late phases (120s later after injection) and, in case of Sonazoid®, also the post vascular phase (starts 10 min after injection). A low mechanical index (MI) (MI<0.3) is usually chosen for continuous real-time imaging.

Detection and Characterization

Many studies have shown that CEUS have greatly improved the sensitivity of US in detecting liver metastases to 80%-90%, which is comparable to the best performance of CT in the literature. Some studies have found that CEUS improved sensitivity by more than 50%, and was especially helpful for metastases smaller than 10 mm [44-45]. Our recent study found that CEUS using high-frequency linear probe could detect more lesions than routine convex probe for the lesions less than 10mm in diameter and located within 60mm below liver surface (89% vs 66%, $p<0.05$), and combining convex and linear probe CEUS, the sensitivity for detection of small CRLMs could reach 97% when taking CECT and CEMRI as golden standard. CEUS using Sonazoid contrast agent could further improve the ability of US in detecting CRLMs, because the liver specific

phase may last for at least 10-30 min and provide adequate time for thoroughly scanning the liver. For detection of malignant FLLs, Sonazoid CEUS presents “defect of enhancement” during the liver specific phase, which makes the detection of suspected malignant FLLs more accurate and easier than CEUS using SonoVue, and even comparable to CECT^[46-48]. Although CEUS has greatly improved the ability US in detection of FLLs by showing the hemodynamic difference between FLLs and liver parenchyma, the performance still depends on the operator expertise, the patient’s habitus (fat and body mass index) and intestinal gas, just like US.

With regard to the characterization of CRLMs, arterial contrast distribution is most important, since most majority of CRLMs present “defect of enhancement” during portal and late phase. Some researchers considered that the arterial contrast enhancement pattern should be relevant to the blood supply of primary tumor^[7]. The generally accepted opinion is that metastasis from hypovascular tumors usually show peripheral enhancement while metastasis from hyper-vascular tumors mostly show homogeneous enhancement. The most common CEUS pattern of CRLMs is rim-like hyper-enhancement in the arterial phase with contrast washout in the portal and late phases (Figures 2-3). However, for the small metastases, especially those after chemotherapy, the blood supply and the enhancement pattern is always atypical. The lesions can be homogenous hyper-enhancement (Figure 4); inhomogenous hyper-enhancement or even hypo-enhancement (Figure 5) in the arterial phase. A prospective study^[19] showed that the performance of all techniques (including IO-CEUS, MR, CT, CEUS and PET-CT) may decrease in chemotherapy-pretreated CRLMs patients compared with upfront resected patients. The decrease was significant especially for CECT, PET-CT and CEUS between the two groups of patients, with overall accuracy from 91% to 73% for CECT, 79% to 53% for PET-CT and 85% to 72% for CEUS, respectively. Our recent study compared the performance of CEUS using high-frequency linear probe and routine convex probe in detection of small CRLMs, and found that high-frequency CEUS could observe better contrast enhancement with more details. Among 15 lesions shown iso-enhancement on routine CEUS in the arterial phase, 11 (73.3%) lesions showed hyper-enhancement on high-frequency CEUS, including 4 lesions with peripheral rim-like enhancement, 4 lesions with homogeneous enhancement and 3 lesions with inhomogeneous enhancement. The other 4 lesions located deep in position (over 6 cm) where high-frequency CEUS could not detect. Despite of

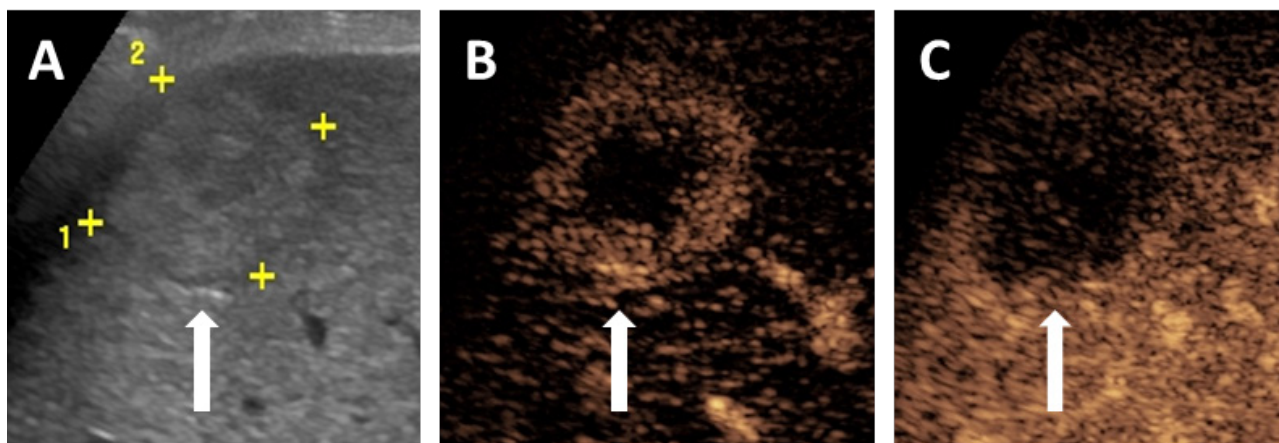


Figure 2 A 80-year-old male patient with rectal cancer. (A) US showed multiple lesions in the liver and the largest lesion (arrow) was surrounded by halo sign with 32 mm in diameter. (B) The lesion (arrow) showed rim-like hyper-enhancement in the arterial phase (22s). (C) The lesion (arrow) washout to be hypo-enhancement in the portal venous phase (75s). The lesion showed typical imaging findings of CRLMs on CEUS.

different enhancement patterns in arterial phase, CRLMs can be detected and characterized reliably as hypo-enhancing lesions during the portal venous, late and post vascular phases, with very few exceptions^[49]. Those consistent enhancement features of metastases

are also helpful in distinguishing metastasis from benign lesions especially in the characterization of small indeterminate lesion on CT or MRI in the oncologic patient. When a nodule shows sustained enhancement on CEUS, metastasis might be virtually excluded^[50].

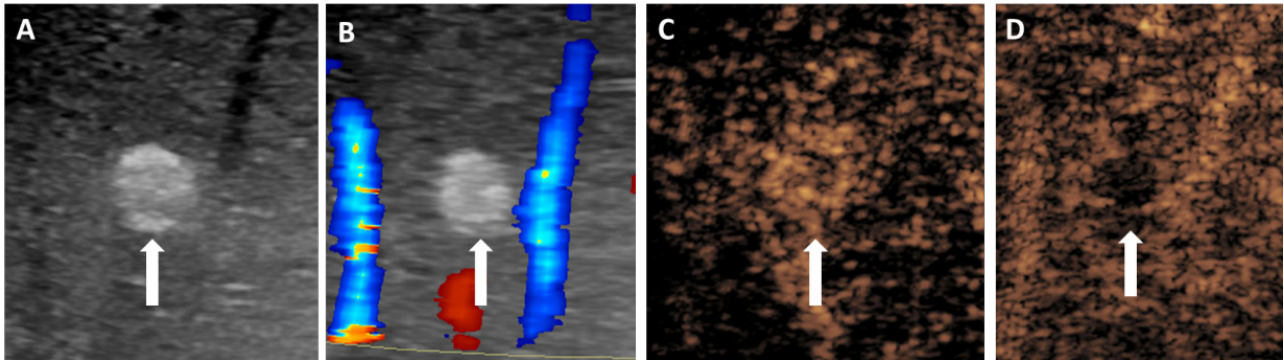


Figure 3 A 37-year-old female patient with colon cancer. (A) US showed one hyperechoic lesion (arrow) in S7 with 7 mm in diameter. (B) There was no obvious blood flow signal in the lesion (arrow) on color Doppler. After baseline US evaluation, it was difficult to differentiate metastasis from hemangioma. (C) The lesion (arrow) showed rim-like hyper-enhancement in the arterial phase using high-frequency linear probe (15s). (D) The lesion (arrow) washed out to be hypo-enhancement in the portal venous phase (108s). The lesion showed typical imaging findings of CRLMs on CEUS.

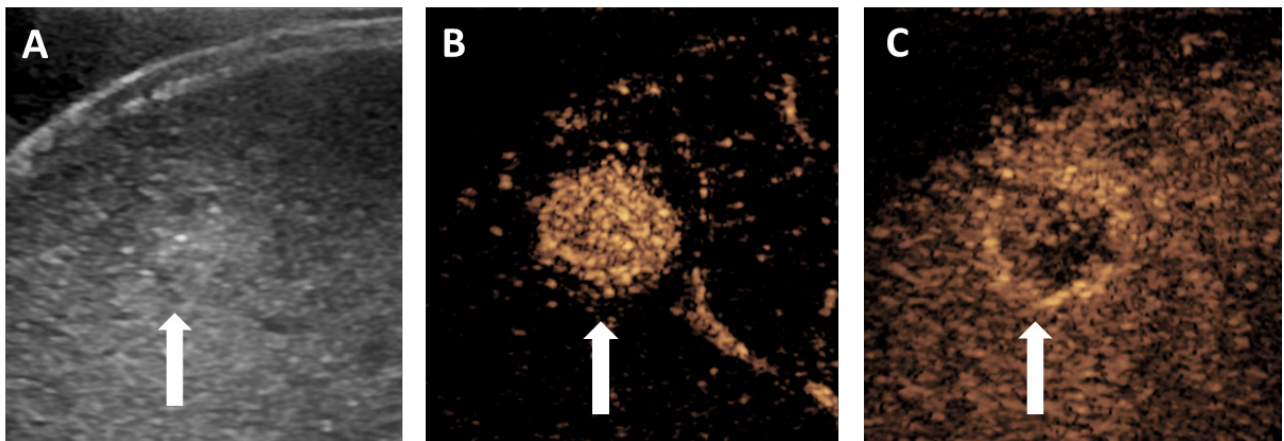


Figure 4 A 51-year-old female patient with colon cancer after chemotherapy. (A) US showed the echo of liver parenchymal was inhomogeneous, and the lesion (arrow) was not obvious. (B) The lesion (arrow) showed homogeneous hyper-enhancement in the arterial phase (14s). (C) The lesion (arrow) washed out to be hypo-enhancement in the late phase (120s). The lesion could be detected and characterized reliably on CEUS.

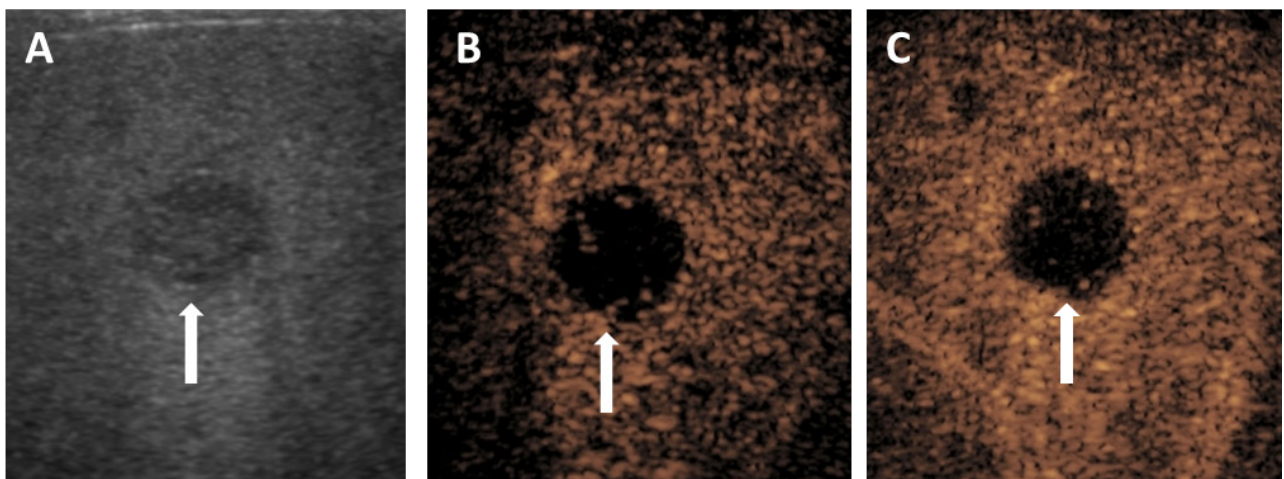


Figure 5 A 38-year-old male patient with rectal cancer after chemotherapy. (A) US showed one hypoechoic lesion (arrow) in S4 with 16 mm in diameter. (B) The lesion (arrow) showed hypo-enhancement in the arterial phase (25s). (C) The lesion (arrow) was hypo-enhancement in the portal venous phase (55s). CEUS performance suggested that chemotherapy inhibited the blood supply of the lesion significantly.

For characterization of FLLs, the contrast enhancement patterns are generally similar among CEUS, CECT and CEMRI^[51]. Nonetheless, occasional instances of discordance occur. Wilson *et al.*^[52] reported the categories of discordance between CEUS and CECT/CEMRI: timing of images, contrast agent diffusion, discordance due to fat and unexplained discordance. Thanks to the real-time scanning capability, CEUS can depict the process of rapid dynamic enhancement of CRLMs, while arterial phase images usually obtained at a single time point on CECT or CEMRI which often miss the early enhancement of the tumor. Since it has been reported that the mean peak enhancement of metastasis on CEUS is at 15s and washout commences earlier than 25s after the bolus injection of UCA^[53]. Rapid and complete washout is an invariable characteristic of metastasis on CEUS, while positive enhancement in the venous or delayed phases might be present on CECT or CEMRI because of the contrast agents leak out into the interstitium of tissues. UCA as a pure blood pool contrast agent, the microbubbles could not diffuse into the interstitium even when the vascular endothelium is highly permeable, and also in case of tumor tissue, in which changes in vascular permeability are commonly associated with tumor angiogenesis^[54]. On US, fat tends to increase the echogenicity of masses containing fat and liver parenchyma with fatty changes. Therefore, when the echogenicity is highly elevated by fatty liver or fat in the nodule, the enhancement level might be erroneously interpreted and result in misdiagnosis. Fat is extremely hypo-density on CT imaging and may significantly increase the contrast between tumor with fat deposition and normal liver parenchyma or decrease the contrast between hypo-intensity tumor and fatty liver on both plain and contrast-enhanced scan. Therefore, the contrast enhancement of target tissue might not be truly displayed, especially for small CRLMs located in fatty liver after chemotherapy. Anyway, in a similar fashion to CECT and CEMRI, CEUS could effectively identify liver metastases, with reported accuracy as high as 90%^[55].

Advantages

CEUS has several advantages over CECT or CEMRI in the evaluation of FLLs^[52]. First, CEUS provides real-time dynamic imaging, which is extremely helpful to visualize a very early or late contrast enhancement of FLLs that may not occur at the predetermined timing of CT or MRI scans. Second, unique intravascular property of the microbubbles UCA may benefit CEUS for characterization of malignant tumors with increased vascular permeability and a large interstitial space, where CEUS could demonstrate the washout phenomenon clearly and consistently, whereas CT or MRI may show prolonged enhancement due to contrast leakage into the tumor

interstitium^[52]. Third, CEUS may also present high contrast resolution due to high sensitivity to the microbubbles and high spatial resolution due to the small field-of-view compared with CECT/MRI^[56]. Forth, multiple injections of UCA are allowed for repetitive observation of tumor enhancement pattern in a single CEUS examination. Fifth, CEUS presents excellent safety profile with a low rate of adverse reactions, and UCA can be used in patients with decreased renal and cardiac function who are not suitable for CECT/MRI^[57].

Limitations

Although CEUS is widely used to evaluate the FLLs, it has some limitations:

(1) CEUS can only observe the performance of one or several neighboring lesions with one injection, which means that CEUS cannot get objective and comprehensive pictures like CECT /MRI.

(2) CEUS is affected by patients' body and the lesion sites, such as subdiaphragmatic lesions, especially those in segment VIII, may not be accessible using conventional CEUS^[28].

(3) CEUS is dependent on operator expertise.

IOUS AND IO-CEUS

IOUS is now considered as a standard method to find preoperatively undetected tumors and determine the resection margin during surgery^[58-59]. IOUS provides high-resolution imaging of the liver and its vascular structures. Deep-seated or nonpalpable lesions can be easily detected by IOUS. The reported sensitivity of IOUS ranges from 85% to 95% in detection of CRLMs^[23]. Moreover, by mapping the major hepatic veins and determining the relationship of the liver lesions to the adjacent vascular structures, IOUS provides real-time guidance for the surgical resection plane. Although IOUS may increase the duration of surgery by a few minutes, it plays a significant role in the surgical management of liver metastases. Some studies showed that findings on IOUS altered the planned surgical approach in 44% to 83% of patients^[26,60]. IOUS can avoid some influence factors of transabdominal US, such as clearly display superficial lesions with high resolution, avoid lung gas interference, avoid the limitations of penetration with scanning flexibly. However, the performance of IOUS is also dependent on the operator's experience, lesion size and echogenicity.

Recent studies of intraoperative contrast-enhanced ultrasound (IO-CEUS) with different contrast agents have shown that it is more sensitive, specific and accurate than IOUS, CT or MRI in detecting and defining whether tumor resection is appropriate^[61-63] (Figure 6). One study showed the sensitivity of IO-CEUS using a linear probe

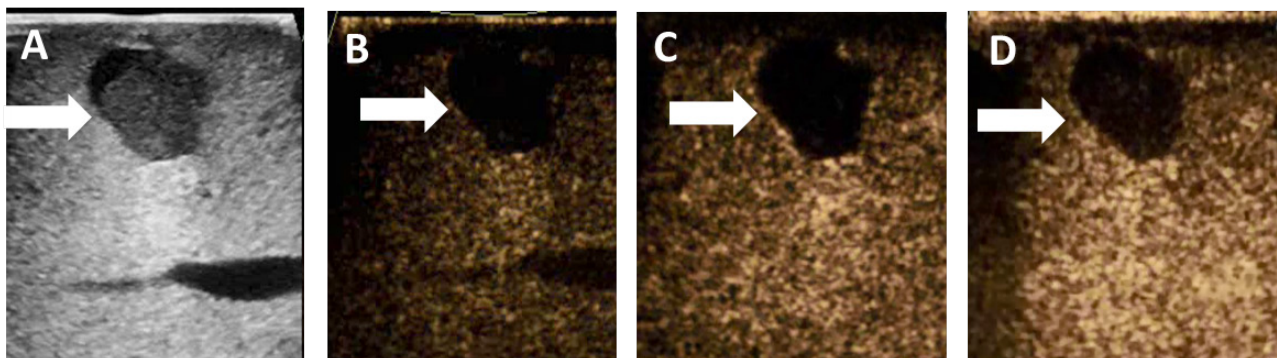


Figure 6 A 50-year-old male patient with colon cancer. A suspected liver metastasis was found by preoperative CECT and CEUS. On IOUS, the hypo-echoic lesion had clear boundary with posterior echo enhancement (A, arrow). However, on IO-CEUS, the lesion presented non-enhancement in the arterial phase (B, arrow), portal phase (C, arrow) and late phase (D, arrow). The diagnosis of benign cystic lesion was established. The final diagnosis of hepatic abscess was confirmed by aspiration.

(6.6 MHz) in detecting tumors less than 1 cm in diameter reached 100%, which was notably higher than the sensitivities of conventional imaging modalities^[64]. Furthermore, surgical management is altered in up to 30% of cases^[61,65-66]. It is now recognized that the more aggressive the surgical approach adopted, the higher the impact of IO-CEUS becomes^[62].

CONCLUSION

US examinations, especially CEUS, are important tools for detecting and characterizing CRLMs. Routine US can be used for preliminary evaluation of colorectal cancer patients and for follow up after treatment. CEUS significantly improved the ability of US examination in detection and characterization of CRLMs, and should be recommended for regular evaluation of colorectal cancer patients in clinical practice. IOUS and IO-CEUS can provide the most accurate results of number, size and location of CRLMs and guide the tumor resection during surgical operation. But all kinds of US examinations have their own limitations, and need to be used in mutual complementation with a comprehensive variety of imaging methods during clinical practice.

CONFLICT OF INTEREST

There are no conflicts of interest with regard to the present study.

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