Focal Liver Lesions: Role of Contrast-Enhanced Ultrasound

Poster No.:	C-2054
Congress:	ECR 2015
Type:	Educational Exhibit
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Keywords:	Cancer, Contrast agent-intravenous, Ultrasound, Oncology, Liver, Abdomen
DOI:	10.1594/ecr2015/C-2054

Learning objectives

1. Describe the most common focal liver lesions (FLLs), as well as their typical contrast enhancement patterns in contrast-enhanced ultrasound (CEUS).
2. Discuss the advantages and disadvantages of CEUS when compared to Computed-Tomography (CT) and Magnetic Resonance Imaging (MRI).

Background

Grey scale ultrasound (US), complemented with colour Doppler, is usually the first line of investigation in the detection of FLLs. However, B-mode US has low sensitivity and specificity when compared to CT and MRI, because of the overlap of the sonographic appearance of benign and malignant liver lesions.

The development of new US contrast agents has considerably improved the possibilities of CEUS in the assessment of FLLs, offering an overall diagnostic accuracy similar to CT and MRI, when US exploration is technically satisfactory and performed by experienced radiologists. Therefore, CEUS is gaining widespread consensus, and knowledge of the CEUS enhancement patterns characterizing liver lesions is very important in the management of these patients.

CEUS has the advantage of the absence of ionizing radiation, the widespread availability and the possibility to characterize a lesion as soon as detected on conventional US.

The factors that limit CEUS are similar to those of basic ultrasound: patients with a poor acoustic window, obese patients, movement artifacts and uncooperative patients. The sensitivity of CEUS is reduced in patients with severe steatosis and deep lesions. It is also impossible to investigate the whole liver with the same degree of sensitivity with CEUS. Furthermore, the arterial and portal phases cannot be simultaneously investigated for multiple lesions. However, the main limitations are the skill and the experience of the performing physician.

Findings and procedure details

Ultrasound Contrast Agents (UCAs) and Safety Issues

Current Ultrasound Contrast Agents (UCAs) consist of microbubbles encapsulated by a stabilizing shell such as albumin, polymer or phospholipid. Microbubbles are miniature gas bubbles smaller than red blood cells, so they easily pass through the capillary beds, acting as blood-pool tracers. In our institution we use Sonovue® (Bracco, Milan, Italy) as UCA. It has a phospholipid shell and a sulfur hexafluoride gas core. Using a non-destructive low mechanical index, Sonovue® allows a vascular-phase imaging of the lesion for several minutes.

Microbubbles are partly removed by metabolism in the liver (stabilizing shells) and partly eliminated from the lungs (with other gases) during the breathing process. Because of this pharmacokinetics, UCAs can be safely administrated without risk of nephrotoxicity. UCAs are generally safe and have lower rates of adverse reactions when compared to contrast agents used on CT or MRI. UCAs are contraindicated in patients with recent myocardial infarction, angina pectoris, heart failure, severe cardiac arrhythmia, right-left cardiac shunt, severe pulmonary hypertension, uncontrolled systemic hypertension and acute respiratory distress syndrome.

Technical Aspects

The performance of CEUS requires contrast-specific software of the ultrasound device that suppresses the signal from the background tissue leaving only the signal from the microbubbles. The technique used to achieve that, is pulse inversion, by which two pulses of sound are transmitted: (1) a pulse is transmitted into the body and echoes are received from the contrast agent and the tissue, and (2) a second pulse that is an inverted copy of the first one is then transmitted into the same direction. Echoes from both pulses are collected by the transducer and linear tissue echoes will nullify each other, while non-linear microbubbles echoes produce a detectable sign.

A low mechanical index (MI) is chosen for continuous real-time imaging in order to minimize microbubble destruction.

Practical Imaging Technique

US investigation starts with conventional B-mode and Doppler techniques. After the target lesion has been identified, the transducer is held motionless while the scanner is switched to low-MI contrast-specific imaging. A dual screen format showing a low-MI B-mode image alongside with the contrast-only display provides improved anatomic guidance.

When using Sonovue®, a bolus of contrast agent is administered (usually 2,5mL), followed by a 10mL saline flush. The diameter of the venous line should not be smaller than 20 gauge to avoid destruction of the microbubbles during their injection.

Immediately after injection, a timer should be started. Due to the specific blood supply of the liver, three contrast phases can be differentiated (table 1). The arterial phase (hepatic artery supply) starts 10 to 20 seconds (sec) after intravenous injection and lasts for 10 to 15 sec. It is immediately followed by portal venous phase which extends from 30-35 sec post-injection to 120 sec. After these, the late phase begins and disappears with the destruction of the microbubbles (about 5 minutes post-injection).

Continuous real-time imaging of the arterial and portal phases is performed, and a video clip of these phases is stored in order to enable a reviewing of the dynamic blood flow features in detail. For the late phase, intermittent scanning may be used until the contrast agent disappears.

	Time post-Injection (seconds)	
Phase	Start	End
Arterial	10-20	25-35
Portal-Venous	30-35	120
Late	>120	Bubble disappearance

Table 1 - Vascular phases of contrast-enhanced ultrasound of the liver

Detection and characterization if FLLs

In the assessment of FLLs the first task is to distinguish between malignant and benign lesions. To do tat, the late phase is the most important of all three phases. Typical malignant lesions, regardless of their appearance in the arterial and portal phase, tend to become markedly hypoechoic in the late phase, whereas benign lesions tend to appear isoechoic or slightly hyperechoic.

The algorithm used to diagnose a liver lesion is summarized in Fig. 1 on page 8.

Benign FLLs

Cystic Lesions

Simple, hemorrhagic and hydatid cysts have a characteristic appearance of clearly defined perfusion defects throughout all phases on CEUS (Fig. 2 on page 9).

Hemangioma

Hemangioma is the most common benign tumor of the liver. It is considered to be a developmental malformation consisting of multiple vascular channels of varying size supported by fibrous interstitium.

In B-mode, hemangiomas display a typical pattern: small, homogeneously hyperechoic, rounded lesions, with distinct margins. When typical hemangiomas are found in patients with no history of malignancy, no additional investigations are necessary. When this conditions are not satisfied, and conventional US is unable to establish the diagnosis, a contrast investigation becomes necessary and CEUS is best suited to immediately follow conventional B-mode.

The typical CEUS findings of liver hemangiomas are peripheral nodular enhancement in the arterial phase and complete or incomplete filling in portal-venous and late phases. Often there is incomplete late filling, especially with larger hemangiomas, which has been attributed to focal scarring or hemorrhagic regions. Centripetal filling-in is more common in medium and large lesions (Fig. 3 on page 10; Fig. 4 on page 10). In smaller lesions (<2cm), the filling-in is more rapid, and the entire lesion may be enhanced at the same level as the surrounding parenchyma, thus, appearing isoechoic in all vascular phases (rapid-filling high-flow hemangiomas). This persistent isoechogenicity suggests hemangioma but cannot be considered completely specific, since it may also be present in other type of focal lesions, such as focal fatty infiltration.

Focal Nodular Hyperplasia (FNH)

FNH is a proliferation of non-neoplastic hepatocytes that are abnormally arranged, as a hyperplastic response to an area of vascular malformation or venous thrombosis, and frequently associated with a central fibrous scar.

FNH is the second most common benign tumor after hemangioma, and is usually discovered in young women. Even if nodules are large in size, they are almost never symptomatic and therefore they usually are incidentally detected. In most cases it is a single lesion, but it can also present with multiple liver lesions.

In B-mode images, FNH is often isoechoic or slightly hyper or hypoechoic. The central scar may be identified as a linear hyperechoic structure. Colour and power Doppler images show the spoke-wheel sign pathognomonic of classical FNH, with often a feeding vessel being evident.

In CEUS, FNH rapidly enhances during the arterial phase with typical centrifugal radiating enhancement. During the portal-venous and late phases, FNH becomes isoechoic or even hyperechoic to the surrounding liver (Fig. 5 on page 10). A fibrous central scar without enhancement is another key feature of FNH.

Hepatic Adenoma (HA)

Hepatic adenoma is a rare primary benign neoplasm found mainly in young women with a history of oral contraceptive use, androgen steroid therapy in patients with glycogen-storage disease. HA may be asymptomatic or present with pain or shock in association with bleeding or tumor rupture. Because of its propensity to hemorrhage and the risk of malignant degeneration, surgical resection is recommended.

Macroscopically, hepatic adenoma is usually solitary and well encapsulated, occasionally with fat and calcifications. Microscopically, it consists of normal or slightly atypical hepatocytes. Bile ducts and Kupffer cells are few or absent.

The characteristic B-mode finding of HA is hyperechoic, hypoechoic or isoechoic heterogeneity. Intralesional hemorrhage initially shows hypoechoic signals. Spotty, sometimes large, calcifications may represent long term evolution of intramural hemorrhage.

In CEUS, HA shows a rapid enhancement in the arterial phase. In the early arterial phase it is often possible to visualize typical peritumoral arteries with centripetal or diffuse filling of the tumor, which is different from the centrifugal enhancement of FNH. The enhancement of HA in the portal and late phases is usually isoechoic, but HA can occasionally show mild washout, remaining slightly hypoechoic in comparison to the adjacent parenchyma. The hemorrhagic regions are avascular and do not show enhancement in any phase.

Focal Fatty Changes or Fatty Sparing

In most cases, the appearance of these areas on conventional US is so typical that no further investigation is necessary. Usually they are polygonal, often with poorly defined margins, located along the portal bifurcation or in close proximity to the gallbladder, and even when relatively large (a few centimeters in size), they do not produce mass effect on adjacent structures. Focal fatty deposit is hyperechoic, whereas focal fatty sparing is relatively hipoechoic in a bright fatty liver.

However, they can be nodular or atypical in location, which may mimic a neoplasm, and contrast imaging is, therefore, recommended to establish a diagnosis. On dynamic imaging (Fig. 6 on page 11; Fig. 7 on page 11; Fig. 8 on page 12), these lesions show no difference in vascularity from the parenchyma. The persistent isoechoic pattern cannot establish a diagnosis of focal fatty deposition since small hemangiomas may also show these same patterns. The lack of mass effect is a useful differential point from neoplasms.

Malignant FLLs

Malignant lesions may be primary or secondary, being the later far more common in patients without cirrhosis. At conventional US, the large number of lesions, a known primary tumor and infiltration of the intra-hepatic vessels or liver capsule, may suggest a malignant nature of the lesions.

As said before, with CEUS, the key feature for the diagnosis of malignancy is a progressive contrast wash-out during portal phase leading to marked hypoechogenicity of the lesion in the late phase (Fig. 1 on page 8).

Hepatocellular Carcinoma (HCC)

HCC is the most common primary malignancy of the liver, most of which occur on a background of cirrhosis.

On grey scale US, HCC may be hypoechoic, hyperechoic or have mixed echogenicity depending on the size of the tumor, the fat content, degree of differentiation and scarring. Therefore, small tumors are usually hypoechoic, but the echo pattern tends to become more complex as size increases.

With CEUS, the majority of HCC show classic enhancement features of arterial phase hypervascularity and later washout (Fig. 9 on page 12). The enhancement pattern is related to the degree of cellular differentiation. Early or well-differentiated HCC have variable degrees of arterial and portal-venous supply, which make these tumors less likely to show arterial enhancement and more likely to be isoechoic in the late phase. Therefore, lack of portal venous washout should not be considered diagnostic of a benign lesion in a cirrhotic liver, as about a half of well-differentiated tumors fail to show washout. On the other hand, moderately or poorly differentiated tumors have fast washout and appear hypoechoic in the portal and late phases. Extended observation (>3minutes) is important to characterize HCC, as in more than half of the HCC the washout occurs after 90 seconds. Note that arterial enhancement may be inhomogeneous, because the tumor

contains septa, regions of different tissue differentiation and shunting among the neo-formed vessels.

Cholangiocarcinoma (CCC)

Peripheral cholangiocarcinoma is a malignant tumor arising from small bile ducts. The appearance of intrahepatic cholangiocarcinoma on conventional B-mode US is not specific. Small lesions are usually hypo or isoechoic in comparison to the surrounding parenchyma, but larger lesions can be heterogeneous. Other common findings of CCC include capsular retraction, satellite nodules, extracapsular extension and vascular encasement within the mass.

Intrahepatic cholangiocarcinoma can have a variety of patterns in the arterial phase: irregular peripheral rim-like hyper-enhancement, heterogeneous hyper-enhancement, homogeneous hyper-enhancement or heterogeneous hypo-enhancement. On CEUS, CCC invariably shows rapid and complete washout within 60 seconds.

Metastatic Disease

The most common malignancy of the liver is metastasis.

On grey scale US, metastases may appear as discrete hypoechoic, hyperechoic or mixed echogenicity, and some may look like target lesions (Fig. 10 on page 13).

On CEUS, metastases show characteristic features in all three phases. Differentiation of hyper from hypovascular metastases is achieved perfectly by real time imaging during arterial phase: hypovascular metastases appear as hypoechoic lesions (e.g. from colo-rectal carcinoma), usually with a typical rim enhancement of varying size, whereas hypervascular metastases (from malignant melanoma, breast cancer, neuroendocrine tumors, renal cell carcinoma) appear as a brightly enhancing hyperechoic and homogeneous lesion. At the beginning of portal-venous phase, the enhancement fades and the entire lesion becomes increasingly hypoechoic. In the late phase, both hyper (Fig. 11 on page 13) and hypovascular (Fig. 12 on page 14) metastases appear as dark defects, whereas the enhancement persists in the normal liver parenchyma. During this phase (late), the lesions are usually particularly well defined, often with sharp punched-out borders.

Images for this section:

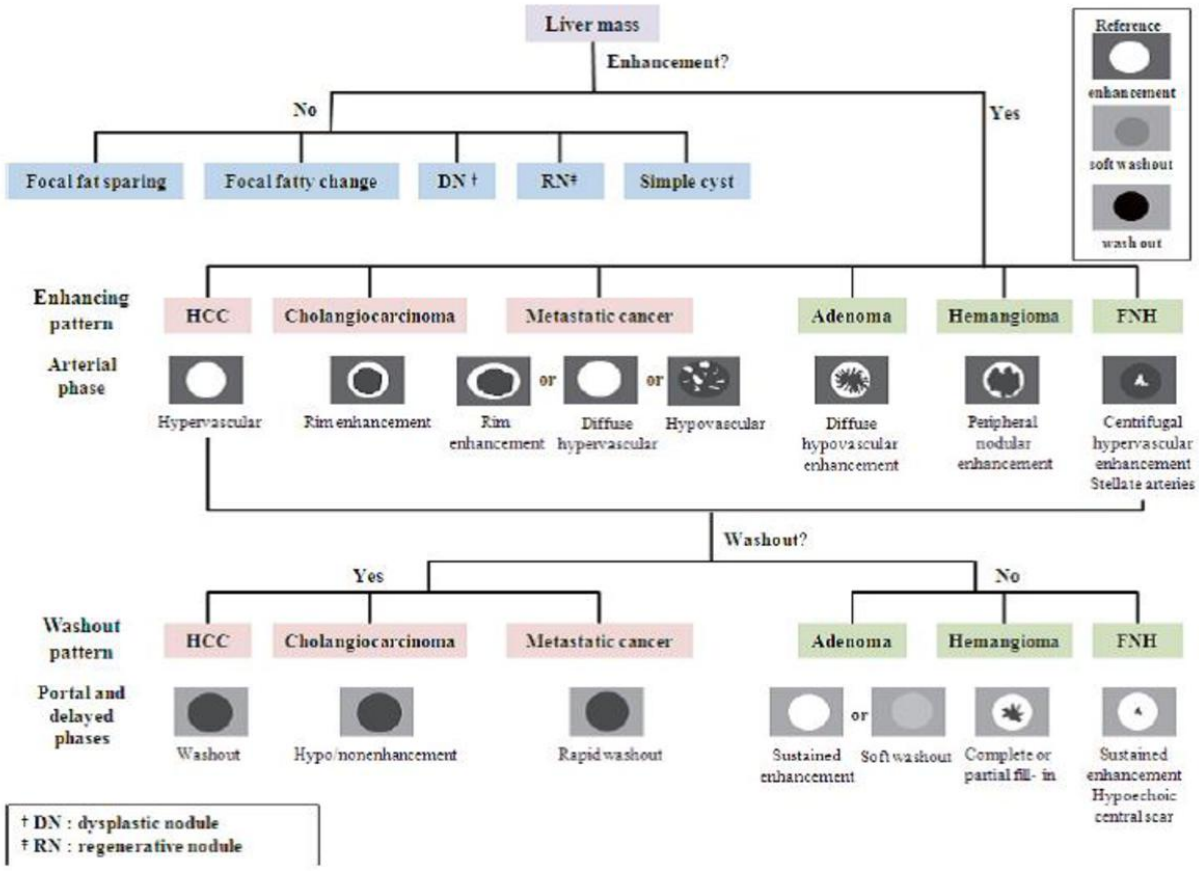

Fig. 1: Algorithm used to diagnose a liver mass

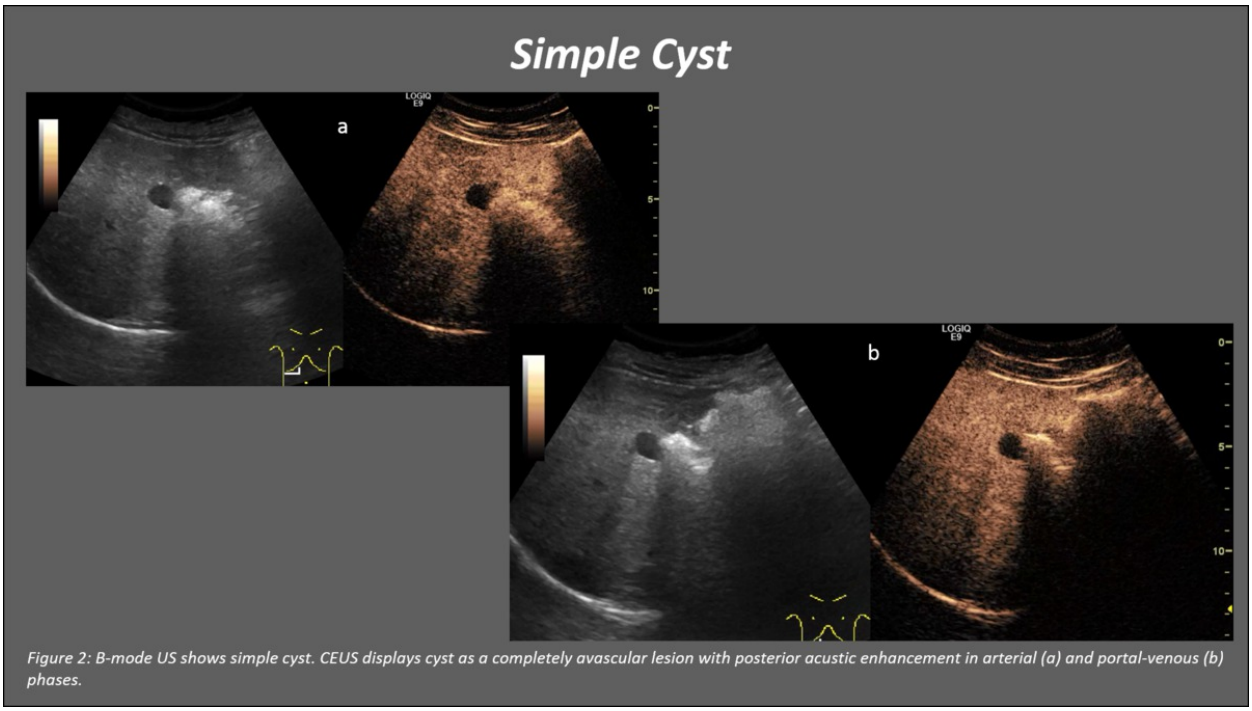

Figure 2: B-mode US shows simple cyst. CEUS displays cyst as a completely avascular lesion with posterior acustic enhancement in arterial (a) and portal-venous (b) phases.

Fig. 2

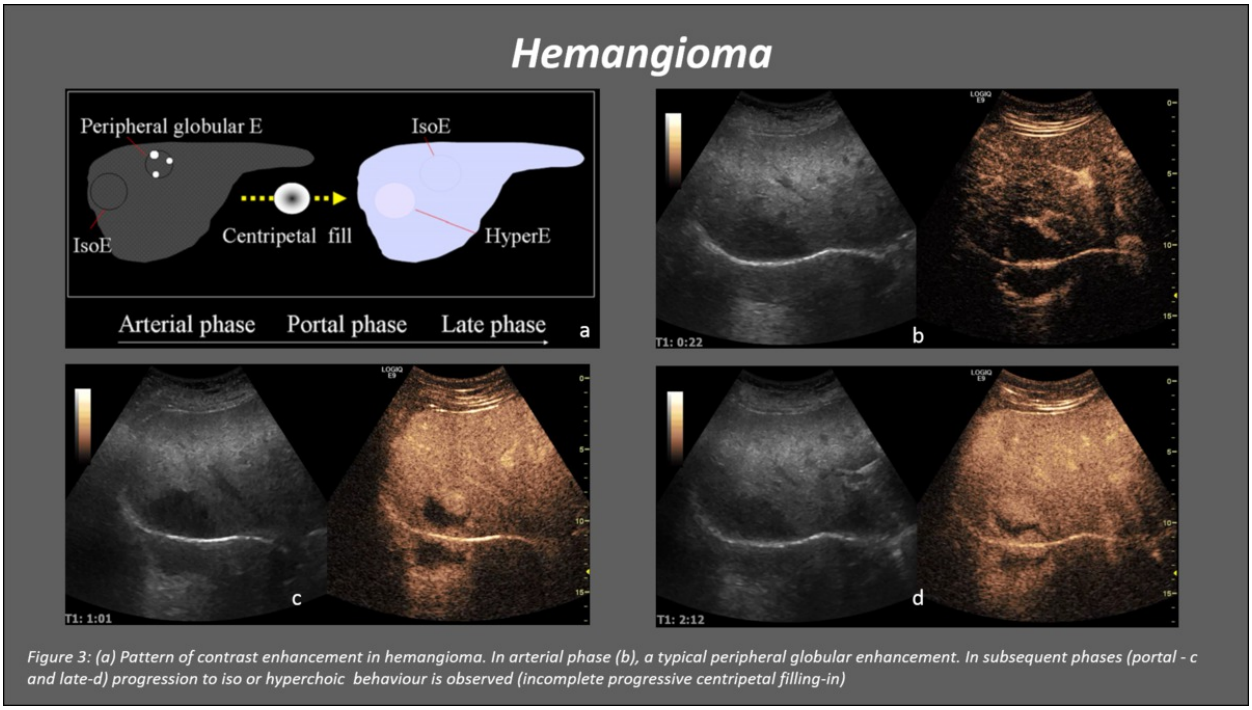

Figure 3: (a) Pattern of contrast enhancement in hemangioma. In arterial phase (b), a typical peripheral globular enhancement. In subsequent phases (portal - c and late-d) progression to iso or hyperchoic behaviour is observed (incomplete progressive centripetal filling-in)

Fig. 3

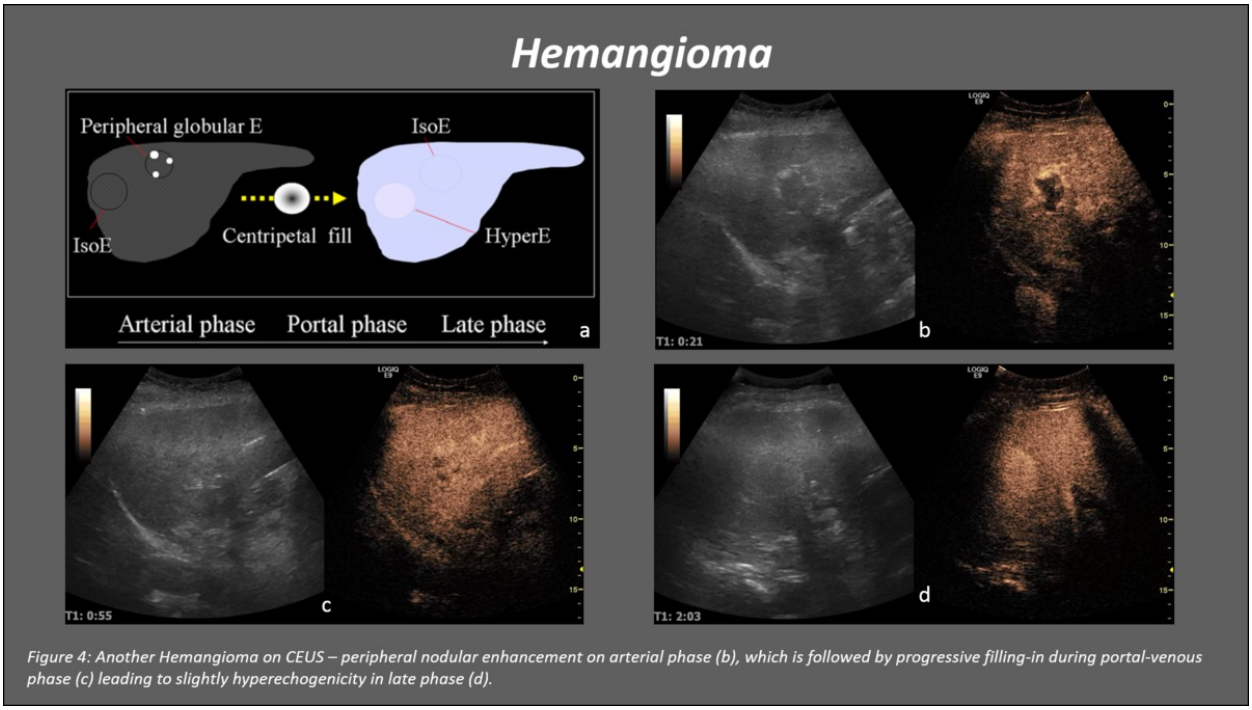

Figure 4: Another Hemangioma on CEUS – peripheral nodular enhancement on arterial phase (b), which is followed by progressive filling-in during portal-venous phase (c) leading to slightly hyperechogenicity in late phase (d).

Fig. 4

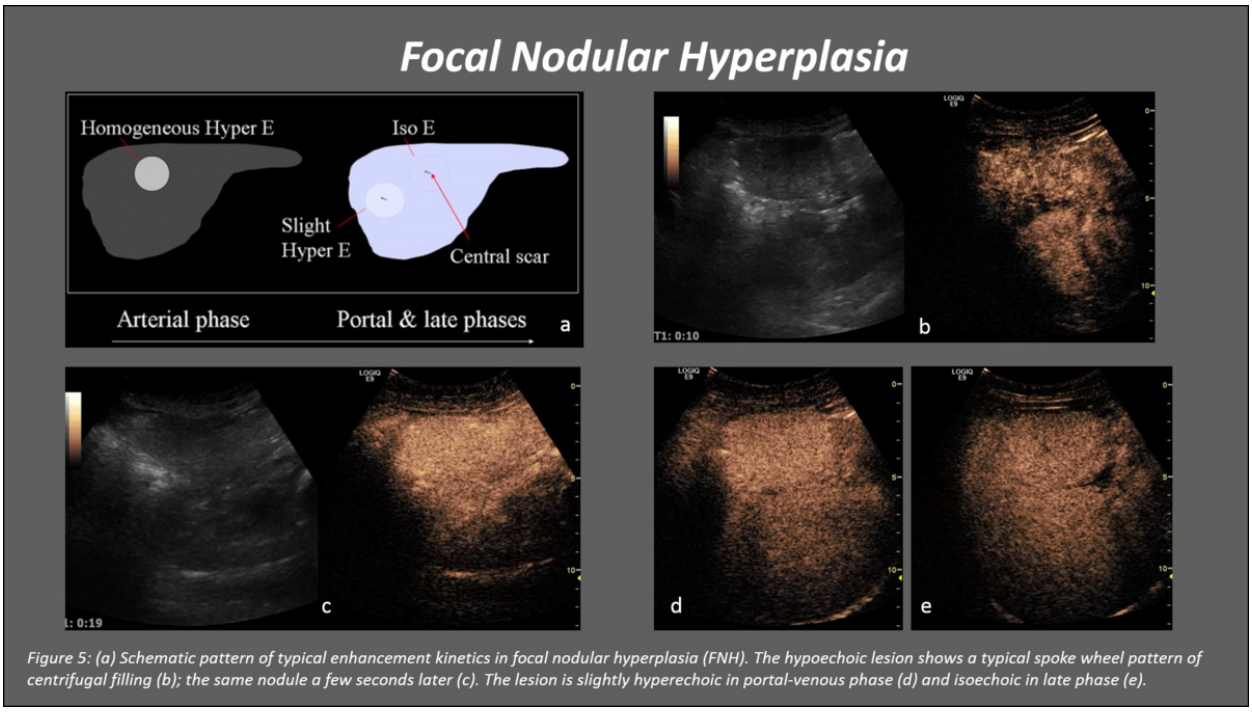

Figure 5: (a) Schematic pattern of typical enhancement kinetics in focal nodular hyperplasia (FNH). The hypoechoic lesion shows a typical spoke wheel pattern of centrifugal filling (b); the same nodule a few seconds later (c). The lesion is slightly hyperechoic in portal-venous phase (d) and isoechoic in late phase (e).

Fig. 5

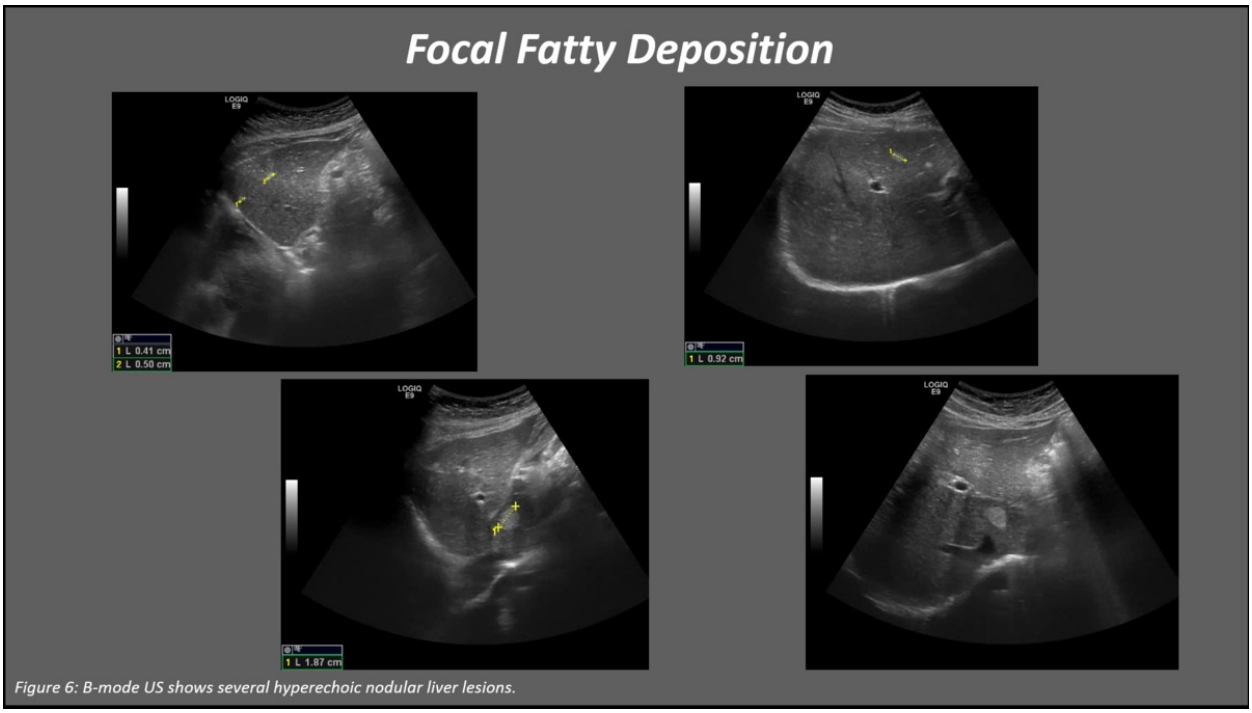

Figure 6: B-mode US shows several hyperechoic nodular liver lesions.

Fig. 6

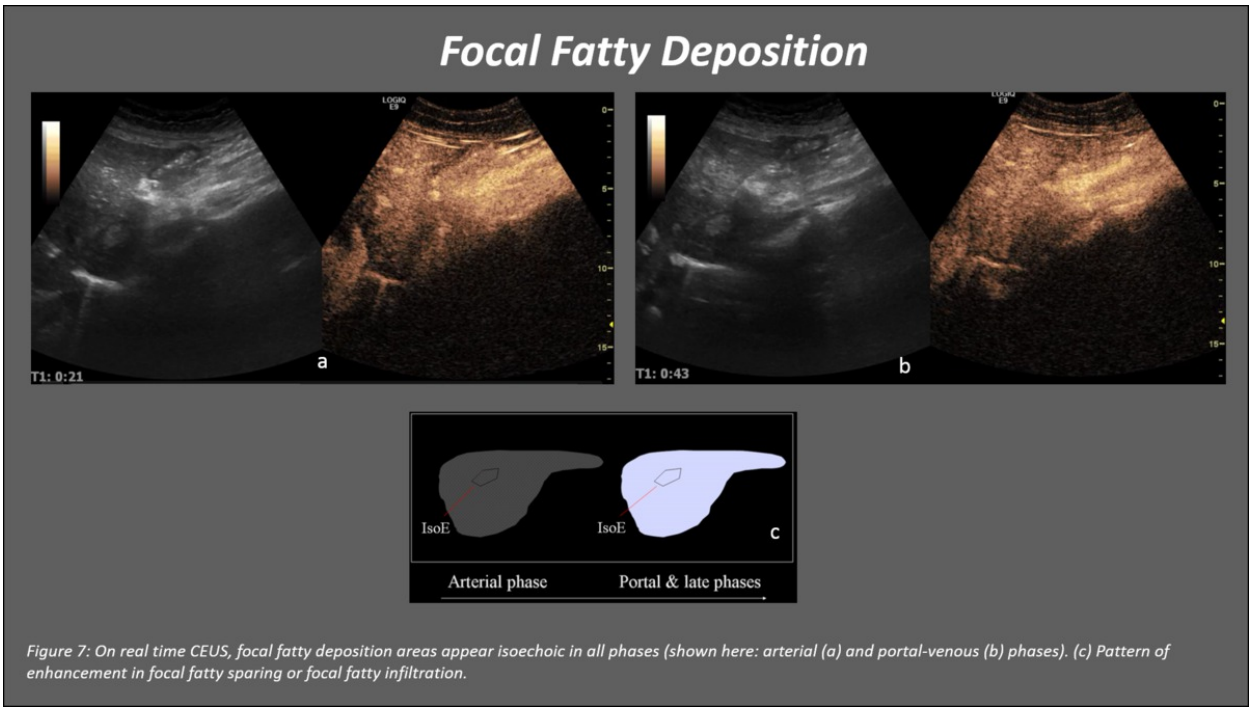

Figure 7: On real time CEUS, focal fatty deposition areas appear isoechoic in all phases (shown here: arterial (a) and portal-venous (b) phases). (c) Pattern of enhancement in focal fatty sparing or focal fatty infiltration.

Fig. 7

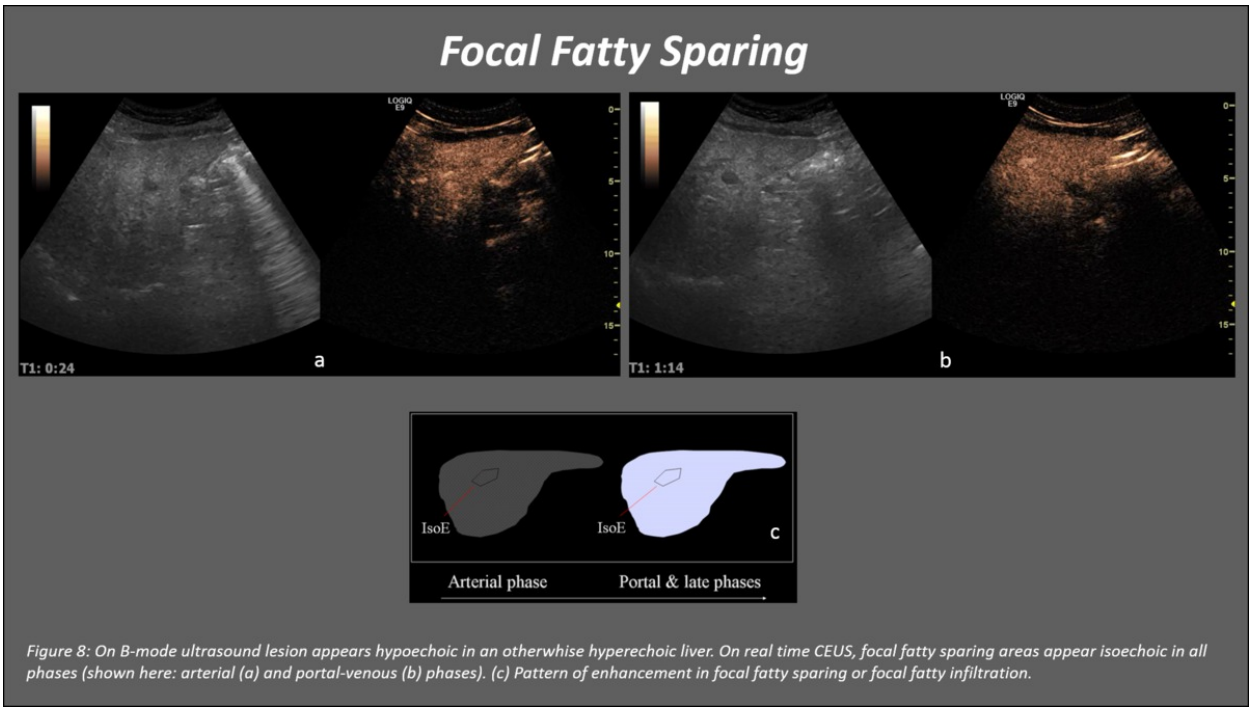

Figure 8: On B-mode ultrasound lesion appears hypoechoic in an otherwhise hyperechoic liver. On real time CEUS, focal fatty sparing areas appear isoechoic in all phases (shown here: arterial (a) and portal-venous (b) phases). (c) Pattern of enhancement in focal fatty sparing or focal fatty infiltration.

Fig. 8

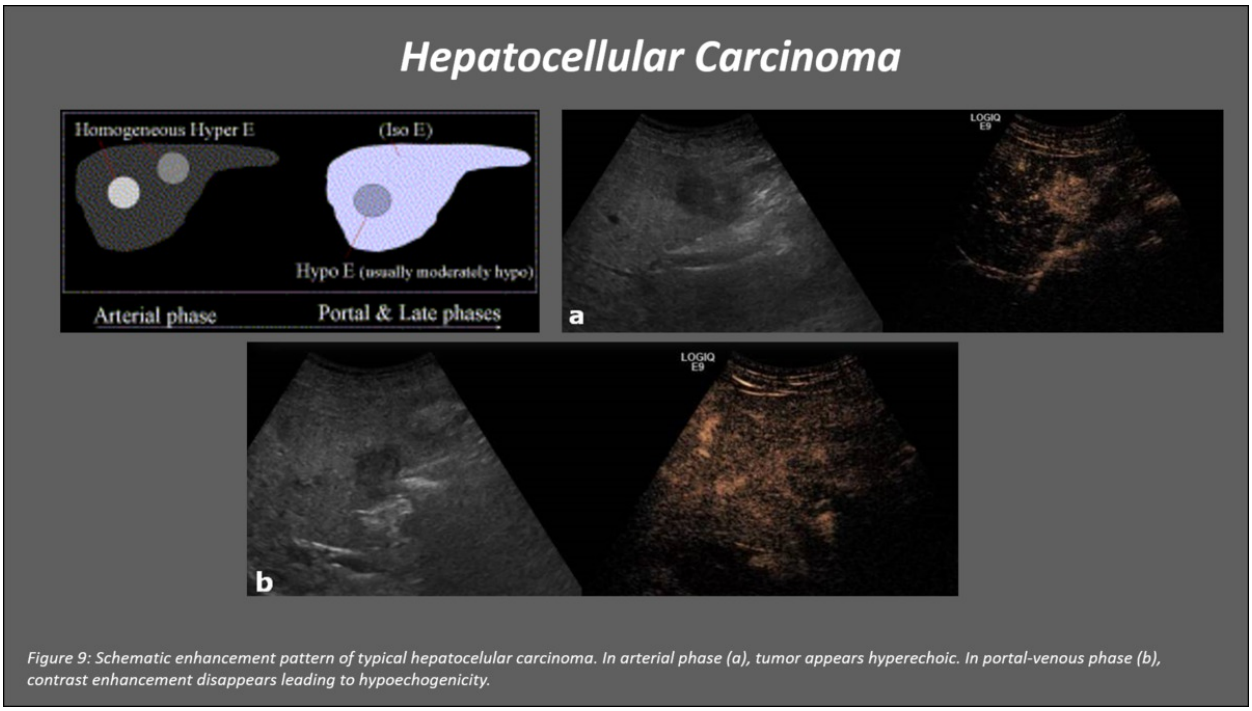

Figure 9: Schematic enhancement pattern of typical hepatocelular carcinoma. In arterial phase (a), tumor appears hyperechoic. In portal-venous phase (b), contrast enhancement disappears leading to hypoechogenicity.

Fig. 9

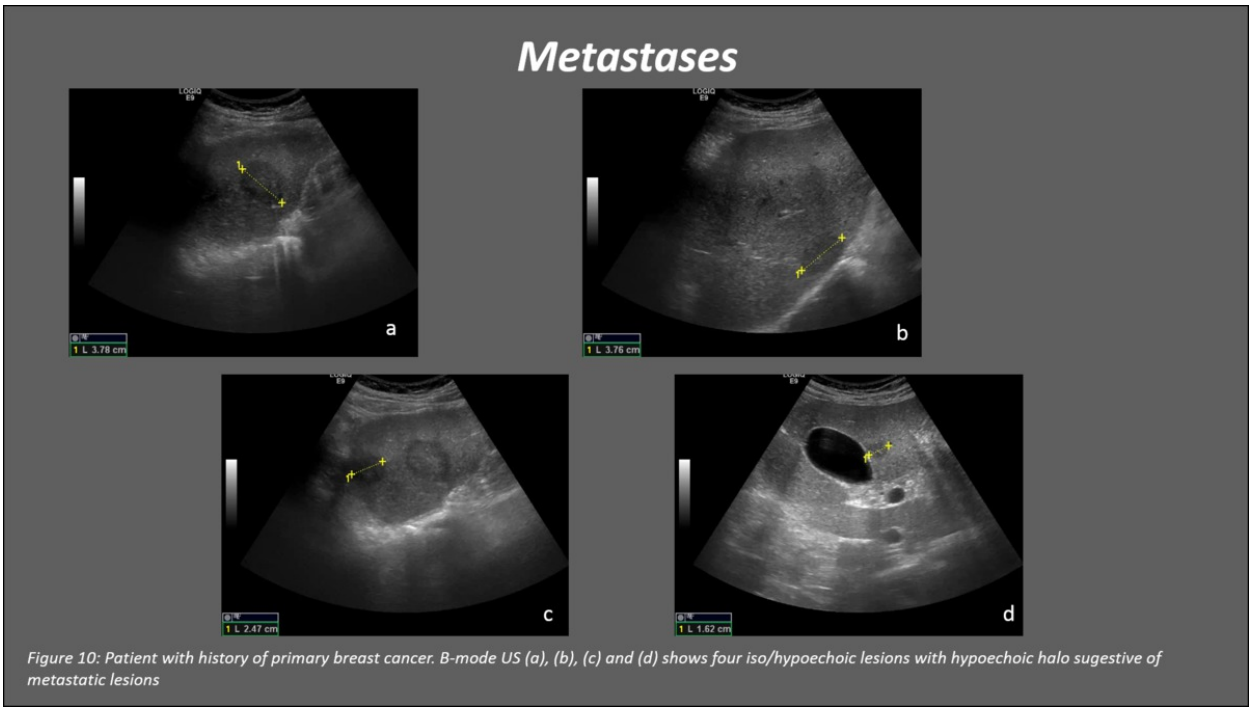

Figure 10: Patient with history of primary breast cancer. B-mode US (a), (b), (c) and (d) shows four iso/hypoechoic lesions with hypoechoic halo sugestive of metastatic lesions

Fig. 10

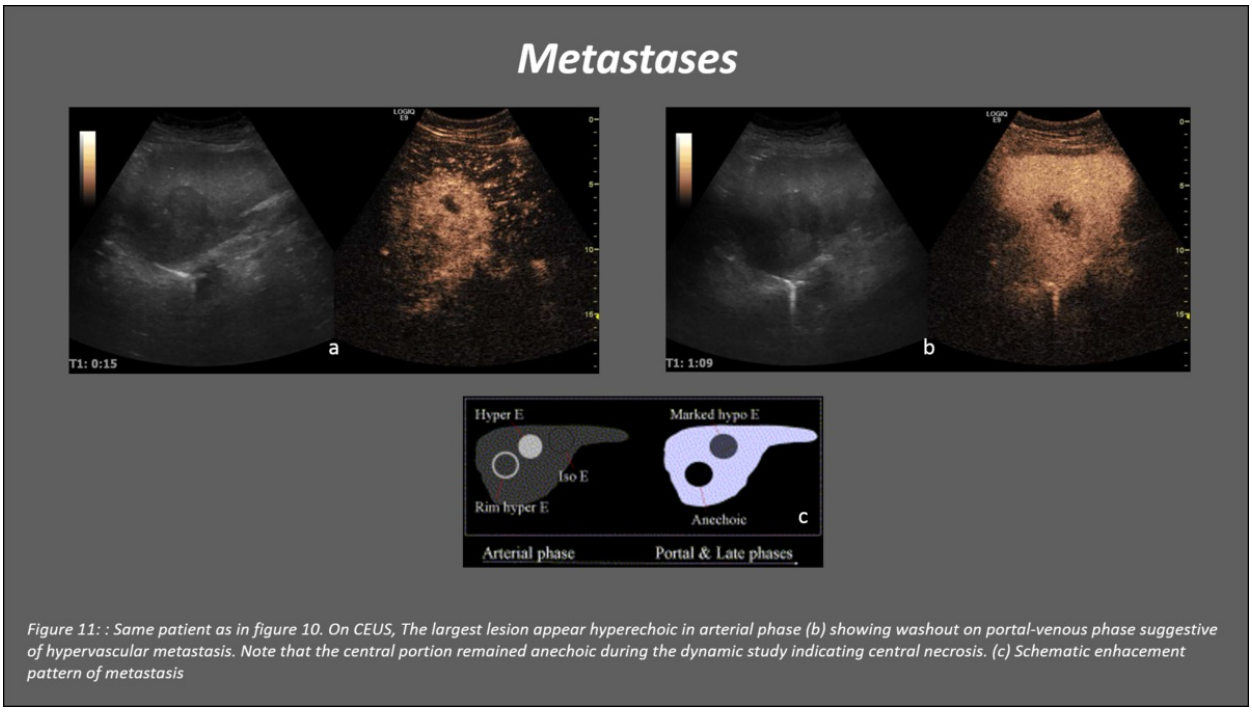

Figure 11: : Same patient as in figure 10. On CEUS, The largest lesion appear hyperechoic in arterial phase (b) showing washout on portal-venous phase suggestive of hypervascular metastasis. Note that the central portion remained anechoic during the dynamic study indicating central necrosis. (c) Schematic enhacement pattern of metastasis

Fig. 11

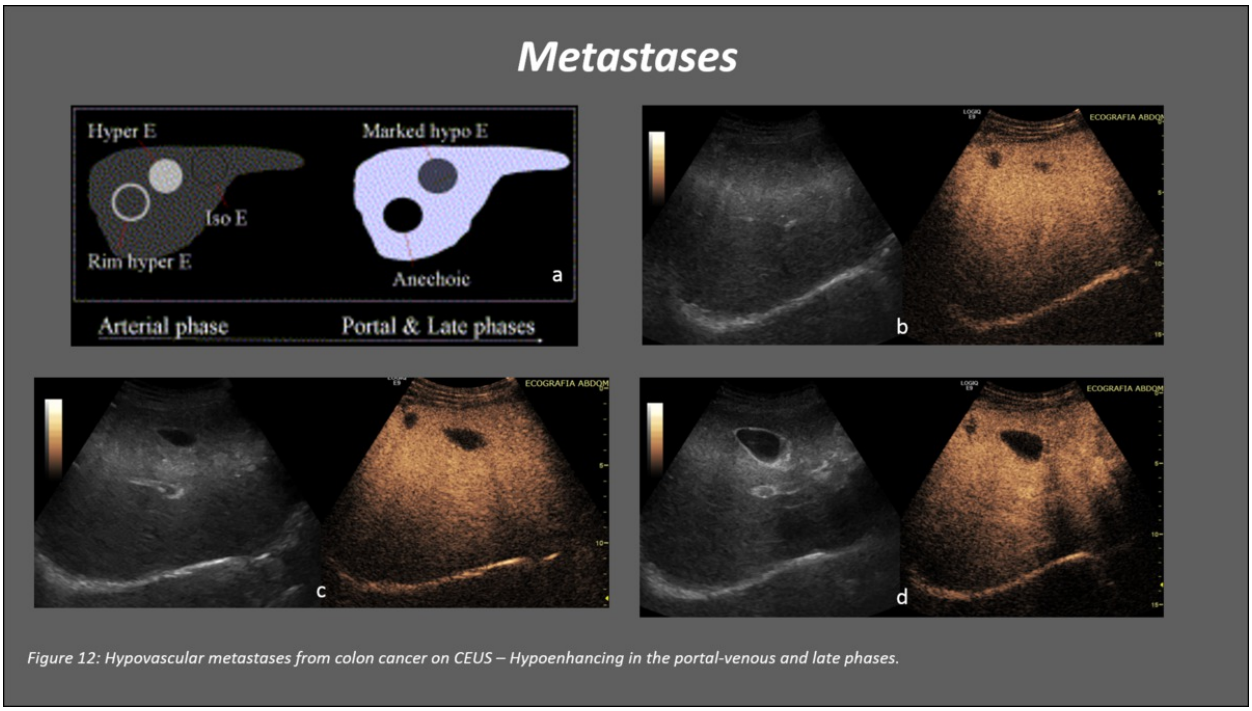

Figure 12: Hypovascular metastases from colon cancer on CEUS – Hypoenhancing in the portal-venous and late phases.

Fig. 12

Conclusion

The introduction of new contrast agents has greatly improved the diagnostic value of US examination. Understanding the typical contrast enhanced patterns of FLLs in CEUS enables to make more accurate characterization.

Despite all the enthusiasm we must keep in mind that the results of CEUS largely depend on the performing radiologist, his experience and the suitability of this method for the particular patient in question.

Personal information

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