The state of contrast-enhanced ultrasound imaging in benign focal liver lesions: Where are we now?

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ABSTRACT

The importance of non-invasive liver imaging is increasing as the epidemic of obesity and liver cancer is becoming a world-wide medical and sociological question. Also, we encounter an increasing number of focal liver lesions due to the widespread availability of conventional ultrasound. The absolute majority of focal lesions are benign in nature and are discovered incidentally. Contrast-enhanced ultrasound (CE-US) can substantially help in a differential diagnostic workup. It has an advantageous cost/benefit ratio, dynamic real-time description of liver perfusion, no radiation exposure and can be executed on most of the US devices. The aim of this narrative article is to demonstrate the characteristic features of benign liver tumors and to show various clinical applications of CEUS.

GENERAL INTRODUCTION

Contrast-enhanced ultrasound of the liver (CE-US) is a diagnostic imaging diagnostic method using a specific contrast agent during US examination [1]. It has been used in several countries for more than a decade, but is still awaiting for more general acceptance in clinical practice. All clinically approved contrast agents (UCA) are microbubbles.

The acronym CE-US refers to contrast-enhanced techniques in general and DCE-US (dynamic contrast enhanced ultrasound) refers to the quantitative time intensity curve (TIC) analysis [2].

Other liver-related imaging techniques, such as contrast-enhanced magnetic resonance imaging (CE-MRI) and contrast-enhanced computed tomography (CECT) are more expensive and include radiation exposure (CT), higher risk of allergies, and have a limited use in patients with renal insuficiency. An absence of real-time imaging in CT / MRI is also a limiting feature. Some MRI contrast agents can initiate a serious generalized fibrotic reaction in at-risk patients.

Conventional US imaging, including Doppler techniques, has some limitations: for instance, it cannnot visualize the liver parenchyma microcirculation [3]. CE-US tries to overcome those limitations, although the spread of CE-US knowledge is rather slow. After many years it was finally approved by the Food and Drug Administration (FDA) in the United States [4], but it is still not generally used in daily routine, as it should be [5]. CEUS has also spread outside its sole use in echocardiology and liver, and the number of CE-US examinations in kidney, prostate, or other GI areas is increasing.

Nowadays, there is widespread availability and use of liver imaging, mainly abdominal ultrasound B-mode and Doppler. The main application of contrast agents (outside cardiology) is for focal liver lesions. There are only few available studies and data on the frequency of focal liver lesions in the general population [6-7]. Focal liver lesions are usually detected incidentally, and about 30% of the general population has one or more benign focal lesion [8-9]. In fact, the majority of all liver lesions found by ultrasoundare benign [10-11]. Most of the incidentally found lesions on US are small simple cysts, hemangiomas, regenerative nodules, focal fatty sparing, and/or focal steatosis. The specificity for a precise lesion diagnosis by conventional US is not very high [10]. Too often, even color Doppler US has limitations in accuracy, sensitivity, and specificity. Benign and malignant lesions can have a very similar appearence. In a case of a typical oval homogenous hyperechoic hemangioma we can probably make a final diagnosis, but in less typical cases US has a limited applicability. In the presence of an underlying extrahepatic malignant disease or in liver cirrhosis, the capability of conventional US to be used to make a diagnosis is even more restricted. In these cases, CE-US can offer improved characterization of liver

lesions [12]. In addition it can also improve the detection of otherwise undetectable lesion (-s) in the liver as is the case of liver metastasis of extrahepatic tumors [13].

In general, there are three main populations for CEUS [10]:
1) general population, mostly healthy persons
2) patients with known oncologic disease, and
3) patients with a diffuse liver disease, including liver cirrhosis.

A typical healthy incidental patient might be a young woman suffering from a common urinary tract infection. Because of infection recurrence, her general practitioner asks for renal and bladder US to be performed. However, an incidental single hyperechogenic oval lesion was found in the liver and requires further diagnostic work-up. The patient receives another appointment, now for a CT or MRI scan in a local hospital within the following 2-3 weeks. These are anxious weeks for the patient, because of unexcluded malignancy. The patient takes a half or whole day work leave, and the technician will perform a CT scan. Usually within another 2–3 weeks, and during another appointment with general practitioner or specialist, the patient will be finally informed about the diagnosis: a benign hemangioma in the liver. An obvious CE-US advantage should the opportunity to perfom contrast examination during the very first US session. The same diagnosis could have been done immediately by performing CE-US. Using the method produces less stress and less expense for the patient and insurance while also no radiation is used in comparison to a CT.

In patients with known oncological diseases, CEUS can achieve comparable results in liver metastases screening to CE-CT or CE-MRI [13-14].

In patients with diffuse liver diseases, the role of CE-US in hepatocellular carcinoma screening in cirrhotic patients and its cost-effectiveness potential still awaits determination [15]. The role of CEUS in characterization of an indeterminate liver lesion on CT or MRI also awaits for a better determination [16]. The role of CEUS in malignant hepatocellular and cholangiocarcinoma is not discussed in this paper.

Initially, a set of guidelines for liver CE-US examination was organized by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) and published in Ultraschall in der Medizin in 2004 [17]. A second and updated edition was published in 2008, reflecting the changes in available contrast agents [3]. The latest document was published in 2013, as a joint update with the World Federation for Ultrasound in Medicine and Biology (WFUMB) [18-21].

Dynamics of CE-US

CE-US allows real-time evaluation of contrast agent wash-in and wash-out in a given region of interest (ROI) over a period of several minutes [22]. All approved contrast

agents are microbubbles, which are several μm in diameter large, and they circulate freely in the capillary network. The microbubbles are gas-filled (sulhur hexafluoride) and stabilized by a shell membrane based on phospholipids and albumin. The contrast agent is a pure blood pool agent [17]. It provides a dynamic visualization of different vascular phases in which the liver has a specific advantage thanks to a dual blood supply and arterial (via hepatic artery) and portal (via portal vein) phases. One can thus diferentiate between three different phases: 1) arterial (AP), 2) portal (PVP), and 3) late (LP). The arterial phase starts within 10 to 20 seconds, lasts approximately 35–40 seconds and is characterized by liver arterial filling. The portal phase starts after 30 to 40 seconds. The time delay and shift are caused by filling of other intraabdominal organs and later entrance into the liver via portal vein. The portal phase lasts for approximately two minutes post-injection. Contrast bubbles fill the liver sinusoids (late phase after two minutes) and during the remaining observation time, the contrast agent is progressively cleared. The recommended observational time is around five minutes, after which the signals start to rapidly deteriorate.

Only US machines with so called nonlinear imaging modes with low mechanical index (MI) for CE-US can be used. Microbubbles act as resonant scatterers, for example, they increase US signal and produce dynamic echoes. Microbubbles resist compression better than expansion. During insonation at a low MI, the expansion and compression are not equal anymore and the returning signal results in the generation of fine non-linear signals, which can be visualized. Under higher energy levels, such as levels used in standard B-scan US, a bubble disruption occurs. In the case of disruption, the result is a strong but short transient signal. This technique was used years ago with the first contrast agents (Levovist). Specific contrast software in US devices suppresses linear ultrasound signals from adjacent tissues and visualizes mainly non-linear signals originating from microbubbles. The result is a positive dynamic signal only from areas filled by contrast agents [22].

Two main diagnostic features to characterise focal liver lesions are in use: 1) vascular architecture and 2) changes in contrast enhancement of the lesion compared to surrounding liver tissue. Vascular architecture is visualized during the early wash-in phase, and lesion changes comparedto adjacent tissues can be viewed during the entire course (wash-in, wash-out) [23].

Some new generation contrast agents (perfluorobutane, Sonazoid) are phagocytosed by the Kupffer cells in the liver. Those cells are residential macrophages in the liver sinusoids. The intracellular phase (post-vascular phase) can further improve CE-US diagnostics [24]. The contrast bubble is not a purely intravascular agent anymore. Malignant tumors show contrast defects in the post-vascular phase, while benign tumors display iso-enhancement in the postvascular phase. However, in benign lesions a region of contrast defect is rarely observed due to thrombosis and necrosis [25].

After disruption, contrast agent microbubbles are eliminated mostly by the liver (phosphilipids from shell membrane), and the inert gas is exhaled via the lungs in approximately 10 to 15 minutes [26].

SAFETY

Before performing CE-US, there is no need to plan any laboratory tests (liver or kidney function). Contrast agents are very safe with no hepatotoxic, thyrotoxic, cardiotoxic, or nephrotoxic side effects. In an Italian series of more than 23,000 abdominal patients, anaphylactic reactions, which can be very serious, have been reported with a rate of 0.001% with no deaths [27-29]. The incidence of severe hypersensitivity reaction is lower than with CT contrast agents. CE-US contrast agents can be used in dialysis patients or patients with impaired renal function without risk of contrast agent accumulation. There is no risk of severe fibrotic reaction as is seen with some gadolinium-based MRI agents.

TECHNIQUE, PROTOCOL AND LIMITATION

Firstly, conventional US of the whole liver should be performed [22]. According to the standard protocol, all eight liver segments should be visualized in which focal liver lesions should be searched. Focal liver lesions must be characterized on a B-scan, and their structure, echogenity, relation to surrounding liver structures, and other characteristics should be described according to standard protocol. Color doppler, including tissue harmonic imaging, is part of a liver examination.

Secondly, a sufficiently large needle is placed in the antecubital vein while patient is in the supine position. The best position for the patient should be determined during a pre-contrast examination. A large needle (20 gauge or larger) is important because microbubbles are sensitive to mechanical stress and can be easily destroyed during injection. Also, higher injection pressure during passage should be avoided. A three-way stopcock is preferred because in multiple injections it facilitates saline flushes without syringe manipulation. To avoid bubble destruction by insonation, we can use only a low MI mode on the ultrasound machine, typicaly lower than 0.3.

Generally, 2.4 ml of contrast agent in a bolus injection is administerd in 1 to 2 seconds followed by 5 to 10 ml of saline flush at about 2 ml/sec . The most widely used US contrast agent in Europe is Sonovue (sulfur hexafluoride, produced by Bracco).

Some limitations of CE-US exist. If the general abdominal US is limited because of anatomical conditions (bowel gas, obesity) examination by CE-US will also be insufficient. The scanning conditions and resolution limitations mean that the smallest lesion diameter lies betweeen 3 and 5 mm [30]. A very small focal lesion can therefore be overlooked. There are also areas of the liver, such as SVIII subdiaphragmatical, that are less accessible to conventional ultrasound. Another limitation originates

from attenuated signal penetration and scattering, especially in liver steatosis. Scanning conditions in fibrotic or cirrhotic livers are even less reliable. Both superficial and deeper lesions do not appear well in the picture and indicate that the outcome of CE-US is dependent on both the patient's general condition in addition to the operator's condition. On the other hand, a significant advantage is the opportunity to scan enhancement patterns in real time, with much higher temporal resolution than is possible with CT or MRI

BENIGN versus MALIGNANT LIVER FOCAL LESIONS

CE-US is highly capable of differentiating between benign and malignant liver lesions. The level of accuracy is the same for lesions that are < 2 cm and those that are > 2 cm. CE-US shows sensitivity of 85.75%, specificity of 85.9%, positive and negative predictive values (PPV and NPV, respectively) of 91.6% and 77.1%, respectively, and accuracy of 85.8% [31-32]. The detection of hypoenhancement during the portal or late phase is strongly suggestive of a malignancy in which 91% of malignant lesions show this feature, whereas only 37% of benign lesions show the feature [33].

The presence or absence of preexisting diffuse chronic liver disease is an important factor in while interpreting CE-US results. In patients with liver cirrhosis, all solid lesions should be regarded as potentially malignant, unless proven otherwise. The presence of wash-out in a patient without underlying chronic liver disease is highly specific for malignancy [34].

CYSTIC LIVER LESIONS

Focal cystic liver lesions represent a broad group of benign or malignant lesions. The most common are simple cysts, other benign are infected or hemorrhagic hepatic cysts, abcesses, hematoma, biloma, biliary hamartomas, biliary cystadenomas and many other rare diseases [35]. Malignant cystic liver lesions include biliary cystadenocarcinoma, cystic metastatic disease – typically neuroendocrine, renal, ovary and others [36].

SIMPLE CYSTS

Simple liver cysts are common and usually found incidentally on B-scan US due to US availability and frequent use of hepatic imaging. Generally, they are of no clinical significance [37].

Hepatic cysts can be solitary or multiple. They contain clear fluid and are lined by a single layer of epithelial cells and a thin rim of fibrous stroma. Simple cysts are oval or rounded and completely anechoic with a nearly imperceptible wall. Refraction shadows at the edges indicate typical dorsal US enhancement. They are nonehnancing in all phases of contrast CE-US [38].

Screening liver CT in patients with known extrahepatic malignancy sometimes has difficulties distinguishing simple benign cysts from possible small liver metastasis and too often need confirmation by another imaging method, such as CE-US [13].

COMPLEX CYSTS

Complex cysts are more difficult to characterize, but with a correct diagnosis, malignant versus benign can be diagnosed in 95% of these cases [38], [39]. Malignant tumors have an inclination to show visible washout with hypoechogenic appearence. Benign lesions do not show any enhancement in all three filling phases, and enhancement in portal and/or late phases is sustained.

Biliary hamartoma (von Meyenburg complex) are symptomless and benign cystic malformations of liver parenchyma. They consist of bile ductules in fibrotic stroma. The continuous improvement of liver US technology has made it possible to visualize these structures more often, and the majority are discovered incidentally [40]. On B-scan US, they present small, hyperechoic, sharply delineated lesions without accoustis shadows [41] that are often on the periphery of microcystic or macrocystic liver lesions, sometimes with a hyperechogenic comet tail artifact. On CE-US they behave similarly to other benign lesions in the filling-in parenchymal in addition to the portal phase. Cystic structures show no echo at all.

Infected or hemorrhagic cysts appear as hypoechoic lesions with a lack of internal vascularity [42]. On CE-US, infectious or fluid internal area is not filled-in, and inflammed walls can show some enhancement but no washout as is seen in a malignancy. Other features are variable and include thick fibrotic septations, internal septa, and irregular walls [43].

Cystadenoma and cystadenocarcinoma are solitary complex cysts with thick fibrotic capsules, which are irregular, sometimes even nodular in appearence, with internal septations. Doppler flow might be conspicuous in internal septations [44]. Older literature studies state that CE-US was not helpful in diferentiating between cystadenoma and cystadenocarcinoma [39], [45]. However, in a recent paper, hyperechoic enhancement in the cystic wall, septations or mural nodules in the arterial phase with isoenhancement in portal and late phase was more typical for cystadenoma, and hypoechoic pattern in portal and late was more common in cystadenocarcinoma; thus, the usefulness of CE-US features appears to be the capability to distinguish between these lesions [46].

Echinoccocus cysts (human alveolar echinococcosis), a cestode parasite, are frequently evaluated by US to monitor disease activity. The conditon was only rarely checked by CE-US in the past. In one study, a vascularization pattern was visualized by CE-US in approximately 50% of the cases when compared results from positron

emission tomography (PET)-CT; thus there might be some relationship of with parasitic disease activity and detection on US [47].

ABSCESS AND GRANULOMAS

Proper and correct diagnosis of liver abcsesses is highly important in medical practice. Clinical circumstances often increase vigilance and suspicion with respect to diagnosing abscesses in the liver, including patients with inflammatory conditions, such as appendicitis, cholangitis, and diverticulitis. In the B-mode, abscesses can present a very variable picture because liquefaction and loculation can profoundly change abscess appearances [43]. Sometimes, abscesses contain gas echoes. Margins can be sharp but also irregular or faint. Abscesses can appear heterogenous, homogenous, fluid-filled, or even solid-like. Thick irregular walls with color Doppler flow are sometimes seen. There is rim enhancement in the arterial and portal phases and a tendency toward hypoenhancement in the late phase. This phenomena probably reflects an increase in the blood flow of the surrounding liver tissue. On CE-US, fluid or central debris is always non-enhancing in all three phases, and this phenomenon differs from malignant lesions, which show at least partial filling.

Granulomas can be isoenhancing or hyperenhancing in the first (arterial) phase with washout (later second and third phase) and thus, they blur the booundaries between malignant and benign lesions characteristics [48].

SOLID FOCAL LIVER LESIONS

FOCAL FATTY SPARING AND FOCAL STEATOSIS

Fatty liver refers to various conditions with fat accumulation in hepatocytes. Most fatty liver (steatosis) diffusely involves the whole liver, and occasionally, we encounter local fat deposits [49].

Focal fatty-sparing (focal non-steatosis) is a hypoechoic pseudolesion that is quite common and often located in segment IV close to portal vein bifurcation or gallbladder bed, medial segment of the left lobe adjacent to lig. falciforme, anterior portion of segment I, or posterior portion of segment IV. In comparison with hyperechoic liver parenchyma (picture of liver steatosis), these lesions appear dark [50], [51].

On the other hand, focal steatosis is a hyperechogenic pseudolesion and sometimes presents as a multilobular, mass-like pattern in normal echogenic liver parenchyma. Patients with this pseudolesion often have potential, comorbid clinical conditions, such diabetes mellitus, alcohol abuse, or other metabolic diseases [52]. A focal steatosis does not produce compression of parenchyma (no mass-efect) as it is not a real tumor (fat droplets are intracellular).

On CE-US, the contrast agent dynamic behavior looks the same in all dynamic phases as in other liver parenchyma since there is normal portal and arterial vascularization in the pseudolesion as in the surrounding structures.

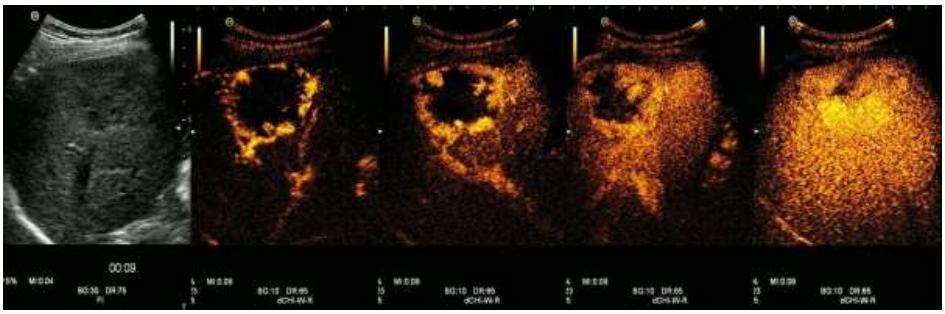
HEMANGIOMAS

Small benign vascular lesions are common in various organs of the body, including the liver. The most common solid benign liver lesions are hemangiomas, and their reported incidence depends on how vigorously they are sought. Their incidence is between < 1% and 20% as incidental hepatic hemangioma when an autopsy is performed [53-54]. The majority of them are small (< 4 cm), asymptomatic and found incidentally. CE-US has improved the accurate diagnosis of hemangiomas, which is now approximately 95% [24], [55].

Typically, hemangioma appearence on B-mode ultrasonography is an oval, round hyperechogenic and homogenous lesion, with well-defined margins, rarely with a small feeding artery and posterior acoustic enhancement. Some are with minimal posterior acoustic enhancement [56]. Doppler flow is too slow to be detected inside the lesion, so Doppler imaging is not useful. In the hyperechogenic surounding parenchyma they can appear either iso- or hypoechogenic.

The typical CE-US pattern is a flame-like or globular enhancement in the arterial phase (PICTURE 1). Contrast agent progressively continues to fill centripetally, and the fill-in is partial or complete, depending on the presence of the thrombus inside the lesion. The filling lasts seconds to minutes, small hemangiomas fill faster.

In a hemangioma during the late phase, there is a typical enhancement, which is sustained for minutes. In some hemangiomas, the filling in the portal or late phase is not complete.



Picture 1. Hemangioma. Baseline ultrasound and CEUS evaluation (a). At B-mode it is not possible to distinct lesion type due to heterogenity of tumor. After contrast administration, slow filling between 15 sec (a) to 1 minute later (e) shows flame-like, centripetal fill-in with complete filling in late phase.

This type of filling occurs mainly in large hemangiomas and probably represents intralesional thrombosis or fibrosis (always avascular). If there is sustained or even progressive enhancement of the nonthrombosed borders during portal or late phases, the lesions are usually of benign in nature. And a hypoechogenic late phase never occurs, and this feature is also a typical trait for benign lesions.

Occasionally, we encounter atypical hemangiomas in which the filling is very rapid and complete, especially when some ateriovenous (AV) shunts are present. Color Doppler is conspicuously strong and usually at the borders of lesion with a strong arterial signal. These types of hemangiomas are the so called high-flow or shunt hemangiomas.

Sclerosed hemangiomas are rare and are characterized by fibrosis and hyalinization resulting from the degeneration of cavernous hemangioma [57]. A filling defect may mimick intrahepatic cholangiocarcinoma in differential diagnosis.

Another atypical feature of this type of hemangioma includes calcifications within the hemangioma.

Sometimes lesions that are isoechogenic in the arterial and portal phases become progressively hyperechogenic compared to the surrounding parenchyma in the late phase [58].

In the differential diagnosis, hypervascular metastasis occurs but usually in this case, the fill-in is very short, and the late phase is completely different (wash-out, hypoenhancement). Another differential is hepatocellular carcinoma (HCC) in which we should also check the portal or late phase (wash-out [59-60]). Sometimes we should wait for 4 to 5 minutes for wash-out to occur in HCC or maybe even longer (so called “late washers“).

HEPATOCELLULAR ADENOMA (HCA)

Hepatocellular adenoma is a benign neoplasm that originates in a normal liver and is composed of cells that closely resemble normal hepatocytes [53]. Older reports of so-called adenomas in cirrhotic liver were very probably examples of macroregenerative nodules.

Adenomas typically develop in women during the reproductive age, and are almost always associated with oral contraceptive use [61]. In our series of 145 adenomas, only 3% were found in men (unpublished data). They have been also reported in patients with an inherited glycogen storage disease and maturity-onset diabetes of the young, and some are obesity-related. Approximately 33%–80% of patients are asymptomatic with tumors discovered by a chance on imaging [61-62]. Recently a new molecular classification has been established, based on metabolic pathways [63-64]. There are currently four suggested subtypes of liver adenomas: 1) Hepatocycte nuclear factor 1 (HNF1-α)- inactivated adenomas (25%–40%, diffuse intratumoral

steatosis), 2) β- catenin mutated (5%–10%, prompted to malignant transformation), 3) teleangiectatic/inflammatory (45%–55%, formery teleangiectatic focal nodular hyperplasia [FNH]), and 4) unclassified (5%–10%). MRI is the best imaging modality for characterizing HCA, and efforts based on MRI imaging are being made to subclassify them in accordance with the above-mentioned metabolic subtypes [65].

On B-mode US, adenomas can be hyperechogenic, isoechogenic or hypoechogenic. They are often homogenous, but previous intratumoral bleeding can change parenchyma into a heterogenous lesion. Sometimes, intralesional calcification can follow an old bleeding episode. On color Doppler US one can find arterial signals with high peak flow and low impedance [66].

HNF1-α inactivated HCAs are often homogenous and hyperechogenic due to fat accumulation. The main feature of inflammatory/teleangiectatic HCAs is heterogenity, which presents an often hyperechoic and prominent Doppler signal similar to FNHs [67]. The other two types (β-catenin-mutated and unclassified) are less characteristically seen on US.

On CE-US, after microbubble injection, adenomas usually show homogenous arterial filling (PICTURE 2), often with a visible feeding artery, and the contrast agent travels very rapidly centripetally from the border to the center part of lesion [68]. In the portal/late phase the lesion becomes isoechogenic, or sometimes faintly hypoechogenic. This event. can even mimic washout and is more prominent in the HNF1-α inactivated HCA subtype [69]. In some patients, this pattern versus a hepatocellular carcinoma can make a diagnosis challenging. An association with hypervascularity, centripetal filling, linear vascularities, peripheral rim of sustained enhancement, and central washout in the late phase teleangiectatic/inflammatory subtype has been shown to exist [69]. These suggestions should, however, be confirmed by other studies [70].

Areas of previous bleeding, thrombi, or necrotic portions remain non-enhancing in all CE-US phases. Higher body mass index (BMI) is associated with the teleangiectatic/ inflammatory subtype and multiple adenomas [71].

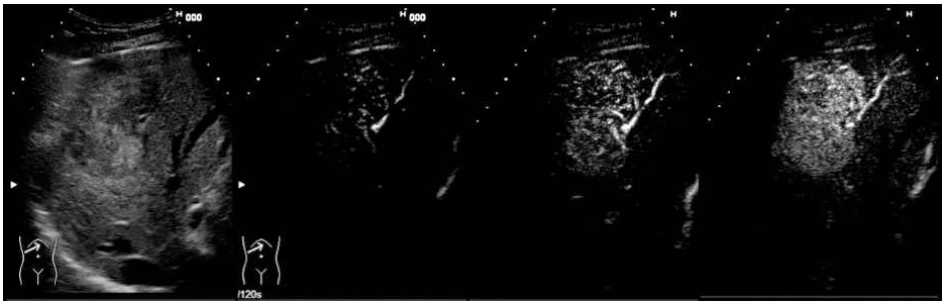
In some cases, a correct differential diagnosis can be challenging against FNH. In adenoma, the centrifugal spoke-wheel pattern is absent, and the central artery with a scar is often more prominent in FNH [72].

FOCAL NODULAR HYPERPLASIA (FNH)

FNH is a tumor-like malformation consisting of hyperplastic nodules of hepatocytes, separated by fibrous septa, which form a typical central scar [53]. The liver is otherwise morphologically and histologically normal. FNH can be defined as not truly a tumor but a local regenerative mass of normal polyclonal hepatocytes (whereas liver

adenoma is a benign monoclonal tumor). The prominent central artery lies close to the central scar.

The lesion is often found incidentally during an imaging session for unrelated complaints. It may be detected more frequently in women (our unpublished data from 184 FNHs suggests 4% incidence in men) and in 15% to 30% of cases, FNH is multiple [73].

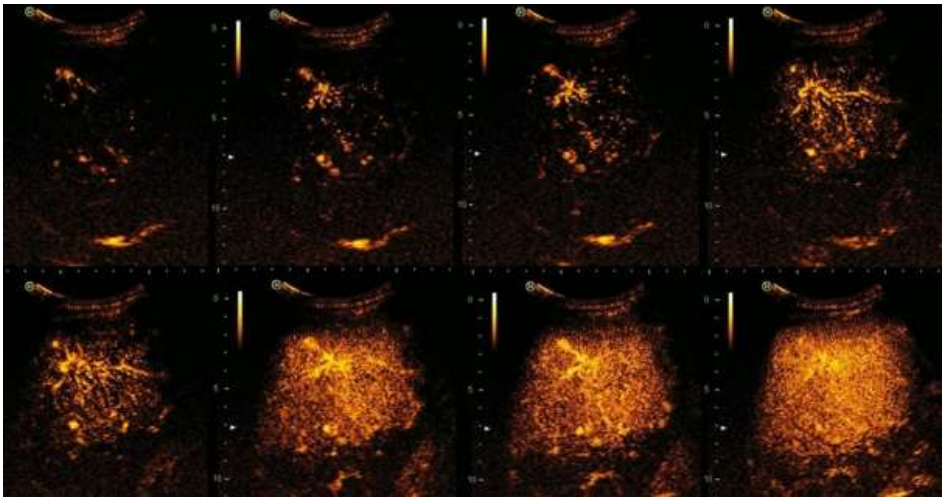


Picture 2: Hepatocellular Adenoma. At conventional B-mode (a) shows heterogenous echopattern. Three CEUS pictures (b-d) show quick filling (sec 10-12). The liver was filled-in portal phase and shows no tumor sings at all (not shown).

In the B-mode, we mostly see an isoechogenic lesion with a central scar and centrally located artery. A fibrotic central scar can be visible as a linear hyperechogenic structure in approximately 70% of the cases. The scar can be very faint, and sometimes multiple scars can be seen. In some patients, a barely visible scar is located more peripherally. The arterial supply can also be multiple or eccentrically located. Central artery imaging can be typical on a color Doppler ultrasound on which it can be seen radiating to the periphery with a high flow and low resistance pattern. FNH parenchyma is usually isoechoic but might be slightly hyper or hypoechogenic.

On CE-US, FNH shows a very short centrifugal spoke-wheel filling pattern in the early arterial phase, which is very rapid, and then is followed by a sustained homogenous faint enhancement during extended observation of the late phase (portal venous) lasting up to 5 minutes [74]. These signs are not present in adenomas. In some patients, FNHs are isoechogenic in the portal or late phase.

The very short nature of rapid spoke-wheel arterial filling is the point at which CE-US shows advantages in time resolution. Recording of the cinematic loop is necessary, and the picture can be checked frame by frame in order to track centrifugal filling of single microbubbles (PICTURE 3).



Picture 3. Focal Nodular Hyperplasia. Typical enhancing filling pattern of a large FNH – centrifugal enhancement within first few seconds in arterial phase.

The central scar appears hypoechoic in the late phase [75-76] and this appearance can be explained by the strict intravascular nature of the ultrasound contrast agent. The central scar is detected in around 40% of the FNHs [77].

The prevalence of typical features of FNH in literature varies considerably from 22% to 70% [64].

Liver adenoma can sometimes display a few fibrotic septa, which in some patients can be a diagnostic chalenge. Lesions originally classified as teleangiectatic FNH are no longer regarded as adenomas. FNH can be also confused with fibrolamellar HCC [1].

Recently, a new technique for quanifying local stiffness has emerged. Shear wave elastography technology can provide additional information from tumors, and FNH is a natural candidate for exploration. In some reports, it has been shown that FNH has higher stiffness compared to other focal liver lesions [78]. Whether focal elastography can be a complementary tool to CEUS or not still waits further validation [79].

REGENERATIVE AND DYSPLASTIC NODULES

Hepatocellular carcinoma develops in a multistep process, consisting of regenerative nodules, low-grade dysplastic nodules, high-grade dysplastic nodules, and early and advanced HCC. HCC is not the topic of this review, but regenerative nodules (RN) are not considered neoplastic lesions, and dysplastic nodules (DN) are considered yet to be premalignant lesions (International Consensus Group 2009). Regenerative nodules can also accompany liver patients with Budd-Chiari syndrome or non-cirrhotic portal hypertension [80].

Large regenerative nodules (macroregenerative nodules) are larger than 5 mm in diameter. If larger, regenerative nodules can be called segmental hyperplasia or lobar hyperplasia , [81]. The initial injury can be subacute hepatic necrosis, vascular injury, or chronic biliary disease. They can be found in both cirrhotic and noncirrhotic livers. On B-scans, they form nodules that are mostly isoechogenic on color Doppler US and display peripheral arterial and venous vessels [82].

On CEUS they show a filling similar to surrounding parenchyma in the arterial, portal and late phases, according to the new classificastion system, LI-RADS®-3 [83-84]. LI-RADS can help inexperienced radiologists obtain substantial consistency in differentiating benign from malignant liver lesions [85].

Dysplastic nodules (low- and high-grades) are nodules in cirrhotic liver that are macroscopically distinct from the surrounding cirrhotic nodules [53]. They are usually larger than surrounding nodules and can be detected via imaging studies. They contain dysplastic atypias without frank malignancy. Low-grade dysplastic nodules (LGDN) may not be distinguishable from large regenerative nodules in that they contain portal areas. High-grade dysplastic nodules (HGDN) have histopathologial features suggesting more cellular proliferation. These modules often present the appearence of nodule-in-nodule formation, but they still contain portal tracts and unpaired arteries, which is a typical feature of hepatocellular carcinoma, that are not yet present. On B-scan US, they can show a mildly hypoechogenic and heterogenous pattern. On CE-US they may show diffuse contrast enhancement and mild hypoenhancement in the arterial phase. Accurate depiction of arterial phase hyperenhancement is vital for distinguishing HCC from dysplastic nodules. Contrast arrival time ratio (CAT_R) can be used in multivariable regression models [86]. In a situation without arterial hypervascularity we rely on portal and late phase washout to diagnose malignancy [87].

In several CE-US studies using the Sonazoid contrast agent, regenerative nodules (RNs) showed centrifugal vessels running from the center to the periphery in the arterial phase (central vessel pattern), and HGDNs showed a centripetal pattern (peripheral vessel pattern) [88-89]. These features also await further confirmation [102].

BUDD-CHIARI SYNDROME

Chronic Budd-Chiari syndrome (hepatic vein thrombosis) often causes the formation of nodular liver lesions that are usually small, multiple, and hypervascular. The majority of them are regenerative nodules and are hyperenhanced in the arterial phase as center-to-periphery or homogenous nodules. In the portal/late phase, nodules showed hyperenhancement [90]. These lesions should be monitored, and some of them can change into HCC, which are seen as heterogenous hyperenhanced lesions in the arterial phase and hypoechoic in the portal and late phases. Other types of

nodules closely resemble FNH due to the presence of a central scar. These nodules are larger than 1 cm in diameter [91].

INFLAMMATORY PSEUDOTUMOURS

Inflammatory pseudotumor (IPT) is a rare benign tumour-like lesion of the liver. It often appears to arise from a healing abscess or other inflammatory condition [53]. This lesion contains a mixture of inflammatory cells with a predominance of polyclonal plasma cells that infiltrate the fibrotic stroma. Diagnosis using imaging studies is difficult because findings vary. There are only a few CE-US-related reports of inflammatory pseudotumors, but they seem to show a quick hyperenhancing lesion in the arterial phase, and some lesions showed quick wash-out in the portal and late phase (fast-in, fast-out) [92-93]. Differential diagnosis should thus include malignant lesions, including liver metastasis and HCA [94].

LIVER ANGIOMYOLIPOMA

Hepatic angiomyolipoma (HAML) is a rare, benign mesenchymal tumor that is more common in women. The tumor may become quite large and usually solitary and is found in a normal non-cirrhotic liver. Malignant degeneration in the liver is extremely rare. Microscopically there is typically an admixture of adipose tissue, thick-walled arteries, smooth muscle and haematopoietic cells [53]. On baseline US they appear as a well-defined, sometimes very large, hyperechoic, and often heterogenous nodule without surrounding hypoechoic halo. Their B-scan picture may resemble a hemangioma. On CE-US, they show heterogenous hyperenhancement in the arterial phase that remains hyper- or isoechoic in the portal/late phase [95]. The arterial filling is often quick and visible vascular signals can lead to a misdiagnosis of FNH [96]. A minority may show a hypoenhancing pattern in the portal/late phase, thus mimicking malignant tumours as HCA [95]. Use of the Sonazoid contrast agent may prove no perfusion defect in the post-vascular (intracellular) phase due to the possible presence of macrophages in the tumor, a phenomenon not seen in malignancies [94]. Quantitative CEUS could be explored in these cases [97].

OTHER

Nodular regenerative hyperplasia (NRH) usually mimics diffuse liver cirrhosis and is not likely to be confused with a neoplasm. Occasionally, in B-mode there may be a large regenerative nodule among small cirrhosis-like nodules, causing confusion with liver adenoma [53]. CE-US should differentiate RNs from HCAs becasue arterial hyperenhancement in the adenoma as opposed to the RN.

The application of CE-US was also described in a variety of other liver focal lesions, such as sarcoidosis [98], epithelioid hemangioendothelioma [99], some tropical diseases [100-101] and others.

CONCLUSION

CE-US was introduced more than twenty years ago and is currently a well-established imaging method, mainly in European and Asian countries. It is highly flexible and free of radiation. The method can be used as a second-line imaging method after a basic non-conclusive B-mode or Doppler liver US session. CE-US performance can result in approximately a 15 min delay in a standard US examination. It is inexpensive and can be performed with medium- or high-end US machines. In many incidentally detected and mostly benign lesions, the final diagnosis can be immediately made and if not conclusive, CE-US is a good begining for imaging studies before other methods are used. Its detection rate is comparable to contrast-enhanced MRI or contrast CT. It is a highly effective method for differentiating malignant versus benign liver lesions. CE-US can also be used in a follow-up examination for primary liver tumors or during surveillance in liver cirrhosis.

The psychological aspect of the patient should also be taken into account as a clinically satisfactory result can often be achieved during the first ultrasound examination.

CE-US and MRI are the best complementary imaging methods and usually present correct focal liver lesion (FLL) diagnoses. When results are inconclusive or suggestive of malignancy, a biopsy can promptly be initiated; thus, additional imaging studies are avoided

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