Solutions in CONTRAST IMAGING
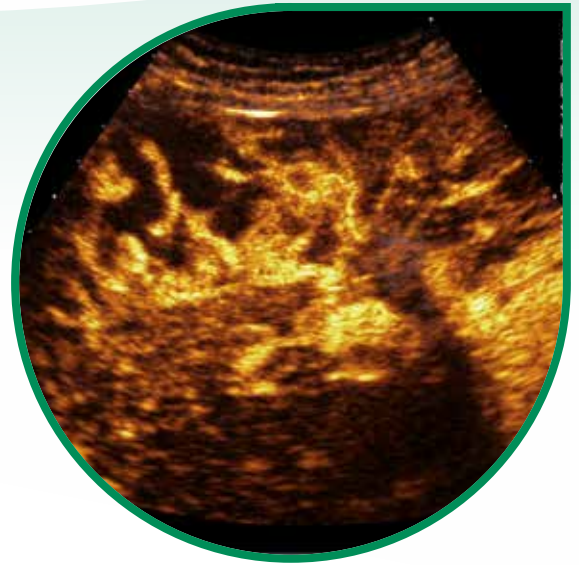

Contrast-Enhanced Ultrasound: Liver Imaging Reporting and Data System (CEUS LI-RADS)

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INTRODUCTION

The American College of Radiology (ACR) endorsed the Liver Imaging Reporting and Data System (LI-RADS) for standardized reporting and data collection of computed tomography (CT) and magnetic resonance (MR) imaging for hepatocellular carcinoma (HCC) in high-risk patients [http://www.acr.org/quality-safety/resources/LIRADS]. The high-risk patient is defined according to the published guidelines. The LI-RADS imaging criteria are used to classify CT or MRI detected 'observations' from 'definitely benign' (LR-1) to 'definitely HCC' (LR-5) based on imaging criteria.[1-7] The term 'observation' refers to an area that is distinctive from the background liver and may represent a true lesion such as an HCC nodule or a pseudolesion such as a perfusion alteration due to arteriovenous shunting.[8] Observations categorized as LR-5 can be managed as HCC without histological confirmation. Category LR-5V is used for definite tumor located within a vein, even if a parenchymal component is not identified at imaging. Category LR-M is used for observations that are definitely or probably malignant, but with imaging features not specific for HCC; the differential diagnosis for such lesions includes atypical HCC and non-HCC malignancies such as intrahepatic cholangiocarcinoma (ICC) or metastases.

Coincident with the recent approval in the United States of a microbubble contrast agent for liver imaging (Lumason®, known as SonoVue® in Europe and elsewhere), LI-RADS is being expanded to include contrast-enhanced ultrasound (CEUS). CEUS is a powerful imaging method that can be used to characterize nodules detected on grayscale surveillance US, or nodules discovered by other methods, including those indeterminate on CT or MR scans.

CEUS LI-RADS is being developed by an international working group of radiologists and hepatologists with expertise in CEUS. The CEUS LI-RADS Working Group was convened in April 2014 by the ACR and has received input from the LI-RADS Steering Committee to facilitate consistency between LI-RADS by CEUS and by CT/MR. CEUS LI-RADS includes the following features:

- a categorization algorithm with well-defined CEUS criteria to reduce imaging interpretation variability and errors, improve communication with referring clinicians and facilitate quality assurance and research [http://www.acr.org/quality-safety/resources/LIRADS]
- an atlas of examples illustrating proper imaging technique, imaging feature characterization, lesion categorization, pitfalls, and differential diagnosis, and
- a lexicon of recommended terminology for use in clinical care and research.

The initial version of CEUS LI-RADS (v2016) was completed by the Working Group and approved by the LI-RADS Steering Committee in July 2016. Sonographically distinct solid nodules ≥ 10 mm in diameter may be diagnosed as definite HCC (CEUS LR-5) if they show both of the following:[9-12]
1) arterial phase hyperenhancement (APHE)
2) mild and late (≥ 60s) washout.

The categorization algorithm of CEUS LI-RADS v2016 is shown in Figure 1.

TERMINOLOGY

The acronym CEUS was accepted as the official term describing contrast-enhanced ultrasound (ultrasonography) techniques in general.[13,14] A separate term is dynamic contrast-enhanced ultrasound (DCE-US) which describes time intensity curve (TIC) analyses used for quantification of tumor perfusion, for example for assessment of treatment response.[15,16] CEUS guidelines were first introduced by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) in 2004, centred on liver applications.[17] The CEUS liver guidelines were then updated in 2008.[18] The current version was a joint venture between WFUMB (World Federation of Ultrasound in Medicine and Biology) and EFSUMB. The guidelines were published simultaneously in Ultraschall in der Medizin/European Journal of Ultrasound (EJU)[13] and Ultrasound in Medicine and Biology (UMB).[14] The CEUS LI-RADS Working Group has adopted the terminology of these existing guidelines and adapted the terminology of CT and MR LI-RADS to CEUS.

Figure 1. LI-RADS algorithm for characterization of focal liver lesions (FLL) in the at-risk patient.
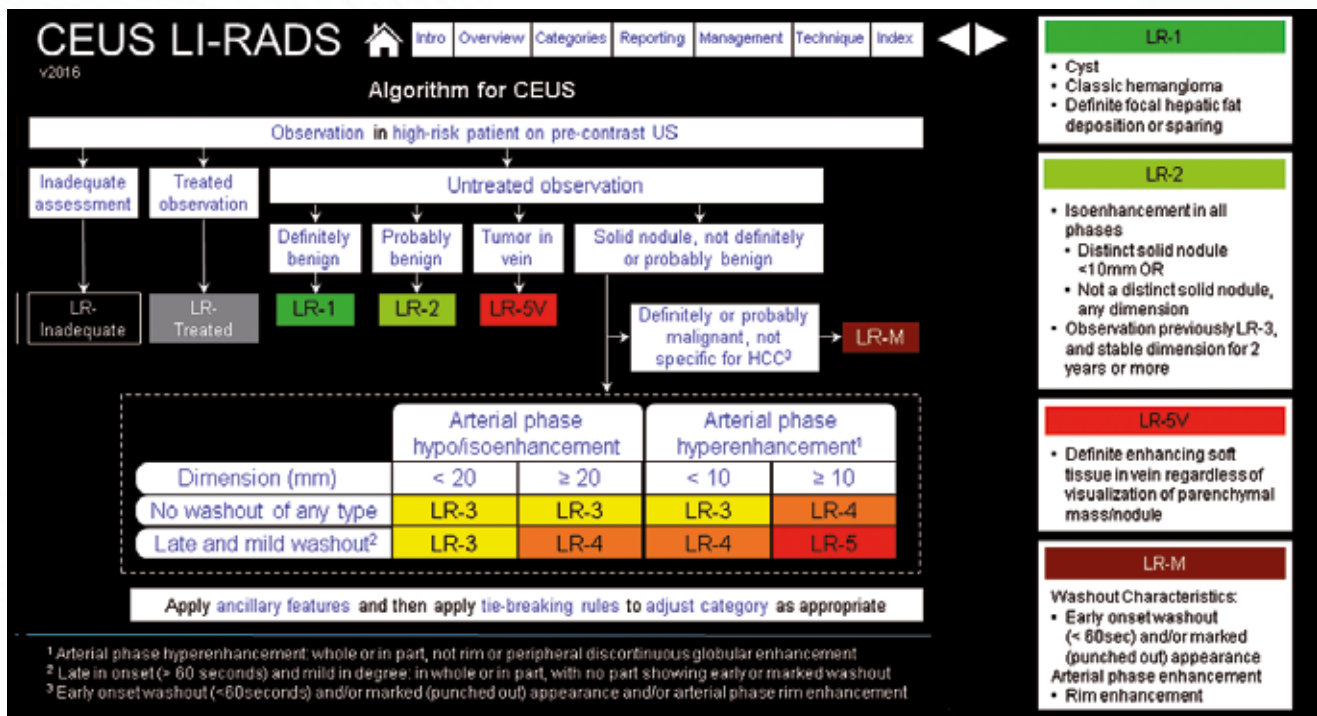
HEPATOCELLULAR CARCINOMA IN THE CIRRHOTIC LIVER

The development of HCC is thought to occur through a multistep pathway in about 90% of cases through the following sequence:
1) regenerative nodule (> 4 mm)
2) large regenerative nodule with low- or high-grade dysplasia
3) dysplastic nodule with a focus of HCC
4) early HCC
5) progressed HCC (the latter two with progressive worsening of tumor cell differentiation).[13,14]

This process of hepatocarcinogenesis is characterized by a progressive increase in arterial flow from newly formed tumor arteries (neoangiogenesis) and a concurrent disappearance of normal intranodular vessels. These newly formed tumor arteries are called 'unpaired' or 'nontriadal' arteries since they are not located in the embryologically derived portal triads and so are unaccompanied by portal veins and bile ducts, and they tend to have a chaotic architecture. Thus, early HCCs typically have greater arterial blood supply than the surrounding parenchyma and less portal venous blood flow. These multistep changes in arterial and portal venous flow are key elements for the characterization of hepatocellular nodules in cirrhosis during the vascular phases of all contrast agents.[13,14,19,20] In parallel with these changes in blood flow, the development of HCC is also characterized by nodule growth. The likelihood of a nodule identified on imaging being an HCC increases with nodule size, from 66% in nodules 10 – 20 mm in diameter,[21,22] about 80% in nodules of 20 – 30 mm in diameter,[23] to above 92% for nodules larger than 30 mm in diameter.

The guideline algorithms for the diagnosis of HCC depend on the contrast behavior and size of the lesion. CEUS LR-5 is a lesion ≥ 10mm in size with CEUS behavior that is typical of HCC, namely arterial phase hyperenhancement and mild and late washout.

INTRODUCTION TO LI-RADS CATEGORIZATION

Characterization of an observation begins as soon as it is detected. On US, benign liver cysts and focal calcifications may be confidently identified and characterized without requiring contrast injection. An HCC may appear on the grayscale examination as a nodule of increased or reduced echogenicity, but may also be occult to grayscale ultrasound or difficult to delineate if it is isoechoic.

Real-time assessment of the arterial phase on CEUS allows detailed analysis of the vascular patterns characteristic of benign and malignant tumors. Portal venous and late phase evaluation of a focal nodule in comparison to the surrounding liver parenchyma will improve differentiation of benign from malignant masses, on the basis of sustained enhancement or washout respectively.[24,25]

SPECIFIC INDICATIONS FOR CEUS

According to the LI-RADS recommendations, CEUS is used in the liver for several reasons to:
- characterize observations (generally ≥ 10mm and visible as distinct nodules at pre-contrast grayscale US) in patients at risk for HCC and establish a diagnosis of HCC
- characterize observations categorized LR-3, LR-4, or LR-M on either CECT or CEMR
- characterize biopsied nodules with inconclusive histology
- contribute to the selection of observation(s) for biopsy when they are multiple or have different contrast patterns
- monitor changes in enhancement pattern over time when a nodule under surveillance is not conclusive for HCC
- differentiate bland thrombus from tumor in vein ("tumor thrombus").

Outside of categorization of observations by CEUS LI-RADS, CEUS is also used for the localization of liver tumors for treatment planning (including transabdominal and intraoperative approaches),[26-30] monitoring local ablative treatment, imaging hepatic vessels (especially in liver transplants), dynamic contrast-enhanced ultrasound (DCE-US) quantification for monitoring antiangiogenic and other types of treatment as well as for other purposes including hepatic transit time measurements and evaluation of the transplant liver.[13,31]

DIAGNOSTIC CRITERIA FOR LI-RADS CHARACTERIZATION

Size. The largest dimension of the liver nodule detected on B-mode ultrasound.

Arterial phase enhancement. The arterial phase enhancement of a liver nodule assessed by comparing the intensity of the signal from a liver nodule with the signal intensity from adjacent liver at the same depth during the peak of arterial phase enhancement (20-40 s after contrast injection).
The type of arterial phase enhancement should be characterized using one of four possible descriptors:
- *hyperenhancement:* higher contrast agent signal intensity in the liver nodule or observation as compared with the intensity in the adjacent liver
- *isoenhancement:* equivalent contrast agent signal intensity in the liver nodule as compared with the adjacent liver
- *hypoenhancement:* less contrast agent signal intensity in the liver nodule as compared with the adjacent liver
- *no-enhancement:* lack of contrast agent signal in the liver nodule.

Washout. Visually assessed reduction in contrast agent signal intensity in a nodule relative to the adjacent liver over time, following initial enhancement, resulting in hypoenhancement. The timing and degree of washout should be characterized.
Timing of washout onset: timing of the first observation of unequivocal washout, reported in seconds after contrast bolus injection.
Washout degree:
- *mild washout* used when a liver nodule becomes hypoechoic relative to the liver but continues to show some contrast enhancement
- *marked washout* used when a focal liver nodule appears virtually devoid of contrast agent signal ("punched out") at a time when the surrounding parenchyma is overtly enhanced. It will look black on CEUS imaging.

LI-RADS CATEGORIZATION

The key feature of CEUS in the diagnosis of HCC in liver cirrhosis is the detection of hyperenhancement of the nodule in comparison to the surrounding parenchyma in the arterial phase (whole or in part, not globular or rim-like), followed by washout in the late phase (late in onset ≥ 60 s and mild in degree), when the nodule becomes hypoenhanced in comparison to the surrounding parenchyma.[9,12,23] This pattern is categorized as LR-5 and is considered diagnostic for

HCC. LR-4 indicates a high probability of HCC, whereas LR-3 suggests an intermediate probability of HCC. Thus patients are managed according to the LR category, keeping in mind that in both cases of LR-4 and LR-3 there is a substantial probability that the lesion is actually an HCC and hence, if the diagnosis is not solved by alternative imaging modalities, histological confirmation may be considered.

CEUS LR-1 (definitely benign)

A liver nodule categorized as LR-1 has imaging features diagnostic of a definitely benign entity. There should be 100% certainty that the observation is benign. LR-1 applies to simple cysts, classic hemangiomas, and some cases of focal fat deposition or sparing; also a previously seen observation that demonstrates definite spontaneous disappearance at follow-up may be categorized as LR-1. Observations interpreted as focal hepatic fat deposition or focal hepatic fat sparing can only be categorized as LR-1 if the CEUS features are unequivocal and/or if the diagnosis was previously confirmed at CT or MR. If there is any uncertainty in the diagnosis, it should be categorized as LR ≥ 2 according to the approved algorithm.

CEUS LR-2 (probably benign)

A liver observation categorized as LR-2 has imaging features that are probably benign, with a high likelihood that the nodule is benign. When in doubt it is recommended to categorize a lesion as LR-3 rather than LR-2.

Examples of LR-2 lesions include:
• distinct solid nodules < 10mm with isoenhancement in all phases
• not a distinct solid nodule of any dimension with isoenhancement in all phases
• nodules previously categorized as CEUS LR-3, and stable dimension for 2 years or longer.

CEUS LR-3 (intermediate probability for HCC)

A liver observation categorized as LR-3 demonstrates imaging features with intermediate probability for HCC. Both HCC and benign entities may be considered as intermediate probability.
Examples include:
• ≥ 10 mm distinct solid nodule with arterial phase isoenhancement without washout of any type
• any size distinct solid nodule with arterial phase hypoenhancement without washout of any type
• < 20 mm distinct solid nodule with arterial phase iso- or hypoenhancement and mild/late washout
• < 10 mm distinct solid nodule with arterial phase hyperenhancement (in whole or in part, not rim or peripheral discontinuous globular enhancement) and without washout of any type.

CEUS LR-4 (probably HCC)

A liver observation categorized as LR-4 demonstrates imaging features probably indicating HCC (nodule is probably HCC but there is not 100% certainty of malignancy):
• ≥ 20 mm distinct solid nodule with arterial phase hypo- or isoenhancement with mild and late washout
• < 10 mm distinct solid nodule with arterial phase hyperenhancement (in whole or in part, not rim or globular peripheral enhancement) with mild and late washout
• ≥ 10 mm distinct solid nodule with arterial phase hyperenhancement (in whole or in part, not rim or peripheral discontinuous globular enhancement) without washout of any type.

CEUS LR-5 (definitely HCC)

A liver observation categorized as LR-5 has imaging features indicating it is definitely HCC (100% certainty nodule is HCC). The criteria are a distinct solid nodule ≥ 10mm with arterial phase hyperenhancement (in whole or in part, not rim or peripheral discontinuous globular enhancement) with mild and late washout (Figure 2).

Figure 2. Typical HCC in liver cirrhosis with hyperenhancement of the nodule (arrows) in comparison to the surrounding parenchyma in the arterial phase (a-d, 26 (a), 30 (b), 40 (c), and followed by mild washout 95 seconds after injection (d) (LR-5). Non-enhancing areas, likely reflecting necrotic zones, are also present.
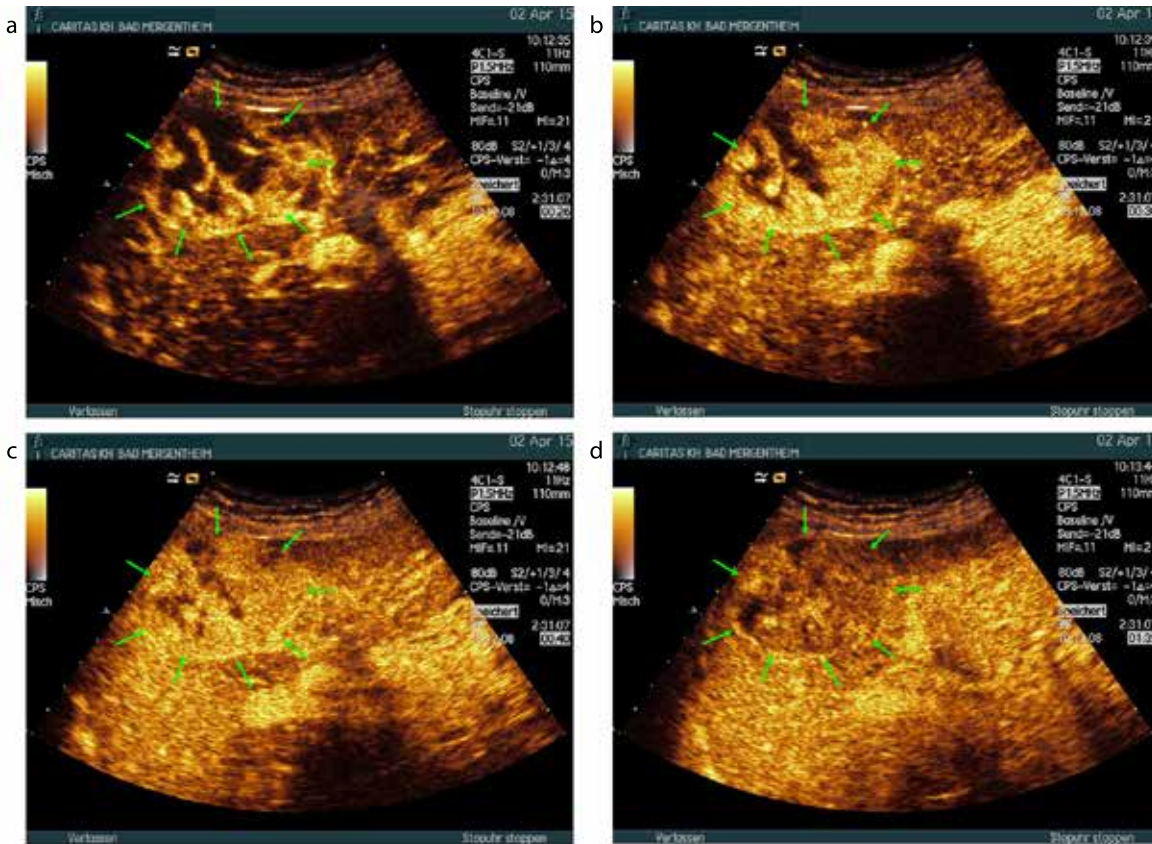
LR-5V (definite tumor in vein)

Liver observations categorized as LR-5V have imaging features indicating there is definite tumor in vein (100% certainty there is tumor within the vein). The criteria are definite enhancing soft tissue in vein regardless of visualization of parenchymal mass/nodule. Late washout is often seen as well (Figure 3). Conventional B-mode features often observed in tumor in vein are disruption of portal vein walls by the tumor and mass-forming aspect of the thrombus.

Figure 3. Typical HCC in liver cirrhosis with definite tumor in vein (a) and arterial phase enhancement of the portal vein thrombosis (b, PVT) followed by washout in the late phase (c).

LR-M (nodule is malignant, but not specific for HCC)

Liver observations categorized as LR-M have malignant imaging features not specific for HCC (nodule is malignant, but not specific for HCC). The criteria are a distinct solid nodule with at least some enhancement in the arterial phase (regardless of morphological pattern or degree) with either or both of the following:
• early washout relative to the liver parenchyma within 60 seconds of contrast injection
• marked washout resulting in a "punched out" appearance.

LR-M is defined by variable arterial phase enhancement including diffuse hyperenhancement, diffuse hypoenhancement, and most often rim enhancement (in the case of metastases and cholangiocarcinoma). The most important characteristic, however, is the washout pattern, showing early onset at < 60 s and/or reaching marked or punched out appearance.

POTENTIAL PITFALLS AND CHALLENGES

Potential pitfalls and challenges of CEUS include, amongst others, heterogeneity from cirrhosis, nodule dimension < 10 mm, subdiaphragmatic or deep location (beyond 12 cm), large body habitus, hepatic steatosis, lack of patient cooperation, interfering bowel gas and artifacts.[32,33]

CHARACTERIZATION OF NODULES OCCULT ON PRE-CONTRAST B-MODE (GRAYSCALE) ULTRASOUND

In select cases, CEUS examiners, at their discretion, can perform CEUS to characterize nodules that are occult on precontrast grayscale ultrasound using anatomical landmarks, image fusion or repeat contrast injections. Such characterization requires substantial experience and expertise. The challenge is to keep the (small) lesion in the image plane although it is not visualized but only presumed on precontrast images, to properly pick-up the contrast washin or washout. This approach is outside the scope of the current CEUS LI-RADS v2016.

SUMMARY

The application of LI-RADS terminology on the use of CEUS for the characterization of focal liver lesions in patients at risk is summarized. Further refinements of criteria and extension to other patient groups is expected in future versions of CEUS LI-RADS.

Key messages

- After the FDA approval of Lumason® for assessment of focal liver lesions the American College of Radiology (ACR) has approved and endorsed a LI-RADS classification system for hepatocellular carcinoma (HCC) in patients at risk based on contrast-enhanced ultrasound (CEUS). This classification system has been developed by an international working group of radiologists and hepatologists with high expertise in CEUS.
- With the release of the latest algorithm, LIRADS now provides standardized terminology, interpretation, and reporting of CEUS in high-risk patients.
- Each modality (CEUS, CECT, MRI) has complementary advantages as well as limitations. Further research is needed to inform the optimal integration of CEUS, CECT, and MRI for imaging these patients.
- In case of observations in high-risk patients made with screening unenhanced ultrasound, CEUS allows an immediate characterization of the lesion in the same session.
- Arterial hyperenhancement and late and mild washout are the key feature of HCC and allow a non-invasive diagnosis of this entity.
- When a diagnosis of HCC is not definitively achieved by CEUS, the algorithm stratifies lesions based on the degree of HCC or other malignancy probability.
- The time of onset and degree of wash-out are essential for the proper classification of observations. Therefore, representative images (or video sequences) should be recorded from all relevant enhancement phases.

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