American College of Radiology
Contrast Enhanced Ultrasound Liver Imaging Reporting
and Data System (CEUS LI-RADS) for the diagnosis of
Hepatocellular Carcinoma: a pictorial essay

Introduction
The Liver Imaging Reporting and Data System® (LI-RADS®) was designed and introduced by the American College of Radiology (ACR) to standardize the reporting and data collection of CT and MR imaging for hepatocellular carcinoma (HCC) [http://www.acr.org/quality-safety/resources/LIRADS]. In 2014, the ACR further identified an international working group of radiologists and hepatologists with expertise in CEUS, including many of the authors of the current article, to establish criteria for CEUS LI-RADS®, in collaboration with the LI-RADS® Steering Committee. A key goal was to harmonize the interpretation of CEUS with that of CT and MR and to facilitate future integration of all imaging techniques for HCC diagnosis. The CEUS LI-RADS® system was officially released by the ACR and published online in September 2016 [http://www.acr.org/quality-safety/resources/LIRADS] (▶ Fig. 1).

All LI-RADS® comprise an algorithm which categorizes observations from LR-1 (▶ Fig. 2), a definitely benign lesion, through to LR-5, reflecting certainty in the diagnosis of HCC (definitely HCC). LR-M suggests a malignant lesion without specificity for HCC and LR-V suggests macrovascular invasion of a portal or hepatic vein (tumor in vein). Between LR-1 and LR-5 are all other possible observations, including hepatocellular nodules reflecting the process of hepatocarcinogenesis, such as LR-2, a probably
benign observation (▶ Fig. 3), LR-3, a observation of intermediate probability for HCC (▶ Fig. 4, 5), and LR-4 (▶ Fig. 6, 7), a nodule with high probability for HCC. The categories LR-3 to LR-5 tend to roughly reflect the progression from dysplastic nodules (> 4 mm) to mature HCC, paralleled by a derangement of intratumoral vascularization (Matsui O, et al. Abdom Imaging 2011;36:264 – 272; Claudon M et al, Ultraschall in Med 2013;34:11 – 29).

The CEUS LI-RADS® working group adopted a conservative approach in order to preserve an extremely high (ideally 100%) positive predictive value for the diagnosis of HCC in lesions characterised as LR-5 (▶ Fig. 8). Therefore, the diagnosis of HCC with CEUS LI-RADS can be trusted with great confidence, and it virtually eliminates the risk of misdiagnosing cholangiocarcinoma. Stringent criteria are required to achieve such high specificity for HCC, which unavoidably reduces sensitivity. Hence, HCCs may occur in other categories, most commonly well differentiated HCC in categories LR-3 and LR-4 and poorly differentiated HCC in LR-M, where diagnoses are achieved by histology, in keeping with the extant hepatology guidelines (Bruix J, Sherman M. Hepatology 2011;53:1020 – 1022; Bolondi L et a, Dig Liver Dis 2013; 45: 712 – 723).

To address the problem of diagnosis of non-hepatocellular malignant lesions by CEUS, which often corresponds to mass forming peripheral cholangiocellular carcinoma (de Sio I, United European Gastroenterol J 2014;2:279 – 287; Wildner D, et al. Ultraschall in Med. 2014;35:522 – 7; Yuan, M. X, Ultraschall in Med, 2016; 37: 609 – 618), CEUS LI-RADS requires meticulous assessment of the timing and degree of contrast washout and of the intranodular contrast distribution in the arterial phase. A rim enhancement distribution in the arterial phase is not typical of HCC and should be categorized under LR-M (▶ Fig. 9). Washout that is mild in degree and late in onset (start ≥ 60 seconds after injection) is consistent with a hepatocellular lesion (Boozari B, et al. Dig Liver Dis. 2011;43:484 – 90; Wildner D, et al. Ultraschall in Med. 2011;35:522 – 7; Yuan, M. X, Ultraschall in Med, 2016; 37: 609 – 618), CEUS LI-RADS requires meticulous assessment of the timing and degree of contrast washout and of the intranodular contrast distribution in the arterial phase. A rim enhancement distribution in the arterial phase is not typical of HCC and should be categorized under LR-M (▶ Fig. 9).
Therefore, depending on nodule diameter and arterial features, a lesion with this type of washout can be categorized LR-5 (Fig. 8). By comparison, washout that is marked in degree and/or early in onset (start < 60 seconds after injection) is non-typical of hepatocellular origin (Yuan MX, et al. Ultraschall in Med. 2016; 37: 609 – 618); regardless of other features, a lesion with this washout pattern is categorized LR-M (Fig. 10). Although the degree of washout is critical to the interpretation, the judgement is left to the operator, since washout degree is influenced by the amount and type of administered contrast material as well as by the ultrasound machine (which may convey different sensitivity to contrast). Investigators from Erlangen recently proposed a CEUS diagnostic system by modifying the CT MRI LI-RADS criteria to incorporate an assessment of washout timing. The Erlangen system does not address the degree of washout (Schellhaas B, et al. Ultraschall in Med. 2016, 2016; 37: 627 – 634), however, thus differing from the official ACR CEUS LI-RADS® criteria [http://www.acr.org/quality-safety/resources/LI-RADS]. Despite addressing only the timing of washout, the Erlangen system was able to provide 75 % positive predictive value for...


Another conservative decision by the CEUS LI-RADS® working group was to require a size threshold of 10 mm for LR-5 categorization. This was done to maintain consistency with CT/MRI LI-RADS®, which does not allow LR-5 categorization for <10 mm observations, while recognizing the difficulty of confidently characterizing such tiny nodules by non-invasive imaging. While not allowing <10 mm nodules to be categorized LR-5 may cause delayed diagnosis in some small HCCs, there is no evidence that delayed diagnosis of small nodules adversely affects patient outcome as long as the patients are monitored closely.

This pictorial essay seeks to familiarize potential users with the system to facilitate its proper clinical adoption. To accomplish this goal, the display reviews the CEUS LI-RADS® algorithm (Fig. 1) and illustrates the spectrum of CEUS LI-RADS lesions. According to the flow chart, the first step is to assess whether the contrast-enhanced ultrasound exam is adequate. Any observations that cannot be assigned a reliable category due to significant problems with contrast injection, lesion depth, liver attenuation, etc., should be reported as LR-inadequate. Treated lesions should be reported as LR-treated (Fig. 11) and are not currently further classified under the LI-RADS® system (this is work in progress from ACR). Presence of enhancing, perfused soft tissue material in any hepatic vessels (hepatic vein or portal vein) corresponds to a tumor in the vein, even in the absence of a clearly detectable parenchymal HCC or LR-M lesion and is characterized as LR-V (Fig. 11). If the soft tissue in the vein does not fit the LR-V category it could be classified as bland non tumor related thrombus (Claudon M et al, Ultraschall in Med 2013;34:11–29).

Subsequently the CEUS pattern of any identified focal observation is analyzed, recognizing that on US, virtually all observations are true nodules (apart from focal fat infiltration or sparing), unlike CT and MR. A pattern corresponding to definitely benign entities such as hemangiomas and simple cysts is categorized as LR-1. Focal fat deposition and focal fat sparing, with classic enhancement characteristics, can also be classified as definitely benign, LR-1. Next, it is judged whether the CEUS pattern corresponds to a definitively malignant lesion, but of uncertain cellular origin which is to be categorized LR-M. The cellular characterization of LR-M lesions requires histological confirmation: it often corresponds to cholangiocellular carcinoma with intrahepatic metastases.
carcinoma, but some lesions categorized LR-M are poorly differentiated or otherwise atypical HCC or quite rarely other rare entities. If a sonographically distinct nodule does not fit any of the previously mentioned categories, then it is likely to be of hepatocellular type and is hence categorized according to its enhancement pattern and size, with increasing probability of being an HCC, from LR-2 (which corresponds most likely to a benign lesion), to LR-3 (intermediate probability of HCC), LR-4 high probability of HCC and LR-5 definitively HCC). Please note that even for LR-2 to LR-3 there is no guarantee that a lesion is not an HCC, even though the probability of HCC is low (most likely a benign lesion) or intermediate, where for LR-4 the probability of HCC is high.

**Conflict of Interest**

Fabio Piscaglia: Speaker fees: Bayer, Bracco; Advisory board: Bayer; Research contract: Esote.  /  Stephanie R. Wilson: Research support: Siemens, Philips; Advisory role: Lantheus / Andrej Lyshchik: Industry grant and Research support: GE, Siemens, Toshiba; Advisory Board: BRACCO; Speaker Panel: SonoScape / David Cosgrove: Speaker and MAB: Bracco Spa, Toshiba, Bk Medical, Clearstream / Christoph F. Dietrich: Advisory board: Hitachi, Mindray; Speaker honorarium: Hitachi, Supersonic, Siemens, Mindray, GE, Bracco, Pentax / Juergen K. Willmann: Research grant: Siemens, GE, Philips, Bracco; Consulting fees: Bracco, Triple Ring Technologies; Advisory board: Lantheus, Bracco, SonoVol / Claude B. Sirlin: Industry grant support: Siemens, GE, Gerber; Consulting and service agreements: Bracco / Yuko Kono: Grant and research support: Toshiba, GE, Philips; Advisory board and speaker fees: Bayer, Wako