Radiology

# State of the Art: LI-RADS for Contrast-enhanced US

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Contrast material–enhanced (CE) US is a recognized imaging tool in the characterization of focal liver lesions and uses microbubble contrast agents to increase signal backscattering from the blood. The European Federation of Societies for Ultrasound in Medicine and Biology and the World Federation for Ultrasound in Medicine and Biology strongly recommend the use of CE US in the characterization of hepatocellular nodules in individuals with liver cirrhosis. CE US was recently approved by the Food and Drug Administration for liver indications in adult and pediatric patients. CE US Liver Imaging Reporting and Data System (LI-RADS) criteria were recently proposed by the American College of Radiology and include eight distinct diagnostic categories: LR-1 (definitely benign), LR-2 (probably benign), LR-3 (intermediate malignancy probability), LR-4 (probably hepatocellular carcinoma [HCC]), LR-5 (definitely HCC), LR-NC (cannot be categorized due to image degradation), LR-TIV (tumor in vein), and LR-M (probably or definitely malignant but not HCC specific). CE US LI-RADS criteria can be used to produce a structured report for HCC diagnosis. However, the variability of US equipment in terms of sensitivity to microbubble signal, interreader variability, large number of HCC nodules classified as LR-3, and wide washout temporal range for LR-M observations are limitations.



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**Learning Objectives:**

After reading the article and taking the test, the reader will be able to:

- Describe contrast-enhanced (CE) US Liver Imaging Reporting and Data System (LI-RADS) classification criteria for different types of observations
- List the different diagnostic categories included in CE US LI-RADS
- List the limitations and potential pitfalls of CE US LI-RADS criteria

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Accurate characterization of hepatocellular nodules in the cirrhotic liver is among the most challenging imaging problems (1–3). Unenhanced gray-scale US and color Doppler US have limitations in the differentiation of malignant from benign liver lesions, especially in the background of liver cirrhosis. The European Federation of Societies for Ultrasound in Medicine and Biology states that contrast material–enhanced (CE) US should be used routinely to characterize incidental liver lesions that remain indeterminate or suspicious for carcinoma after unenhanced US and for every lesion identified or suspected during US surveillance in patients with chronic liver disease and liver cirrhosis or in patients with a known history of malignancy (4). CE US reveals typical patterns of contrast enhancement in the different lesion histotypes (5) and provides comparable overall accuracy in focal liver lesion characterization, higher sensitivity in the recognition of malignancy, and higher specificity in the exclusion of malignancy when compared with CT and MRI (6). The purpose of this review was to describe CE US LI-RADS diagnostic categories, with an emphasis on limitations and potential pitfalls.

## Background: Microbubbles for CE US

CE US involves intravenous injection of microbubble contrast agents. Microbubbles represent a class of contrast agents and have a pure intravascular distribution; a diameter of 2–6 μm; a shell of biocompatible materials, including proteins, lipids, or biopolymers; and a filling gas with low solubility in the surrounding bloodstream (7). The main effect of microbubbles depends on the compressibility of gasses, which is markedly different from the near incompressibility of native tissues, which determines the production of harmonic frequencies, provided microbubbles are insonated by the appropriate resonance frequency (range, 2.4–2.8 MHz). This difference in compressibility can be exploited by using multipulse sequences that cancel tissue signals and emphasize signals from microbubbles with a much higher contrast resolution when compared with that of unenhanced US. This multipulse sequence cancels linear stationary returning waves by sending a reversed incident pulse. These microbubbles resonate under low-acoustic-power US waves and generate harmonic signals that can be detected with specialized contrast material–specific US modes. CE US uses dynamic real-time imaging at a frame rate of 10–15 frames per second and provides a higher temporal resolution than either CT or MRI, both of which are performed according to predetermined fixed timing or are related to timing from a contrast material bolus in the aorta. This represents a

## Abbreviations

CE = contrast enhanced, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma, LI-RADS = Liver Imaging Reporting and Data System


## Summary

In this review, the appropriate use of contrast-enhanced (CE) US to characterize hepatocellular nodules in patients at risk for hepatocellular carcinoma is presented along with Liver Imaging Reporting and Data System criteria that enable standardized reporting of CE US results, with an emphasis on limitations and potential pitfalls.


## Essentials

- Contrast-enhanced (CE) US Liver Imaging Reporting and Data System (LI-RADS) criteria can be used to produce a structured report for diagnosis of hepatocellular carcinoma (HCC).
- CE US LI-RADS criteria include eight distinct diagnostic categories: LR-1 (definitely benign), LR-2 (probably benign), LR-3 (intermediate malignancy probability), LR-4 (probably HCC), LR-5 (definitely HCC), LR-NC (cannot be categorized due to image degradation), LR-TIV (tumor in vein), and LR-M (probably or definitely malignant but not HCC specific).
- The variability of US equipment in terms of sensitivity to microbubble signal, interreader variability, large number of HCC nodules classified as LR-3, and wide washout temporal range for LR-M observations are limitations.

clear advantage of CE US over CT and MRI, as CE US may depict both early and late contrast enhancement that might be missed at CT or MRI because of mistiming. In addition, the spatial resolution of CE US is higher than that of CT because of the limited field of view of CE US at the same digital image matrix size.

In Europe and the United States, two commercially available US contrast agents are suitable for characterization of focal liver lesions: SonoVue (Bracco, Geneva, Switzerland) and Definity (known as "Luminity" outside the United States and Canada) (Lantheus Medical Imaging, Billerica, Mass). SonoVue consists of microbubbles with the inert gas sulfur hexafluoride ($SF_6$) and a phospholipid shell monolayer, while Definity consists of microspheres with an outer lipid shell that encapsulates perflutren. Recently, SonoVue was approved by the Food and Drug Administration under the name Lumason (Bracco Diagnostics, Monroe Township, NJ) for use in the characterization of focal liver lesions in adult and pediatric patients and in the evaluation of suspected or known vesicoureteral reflux in pediatric patients (8). Definity is approved in Europe and Canada for suboptimal echocardiography to improve the delineation of the left ventricular endocardial border, and it is approved in Canada for liver and kidney imaging in adult patients. Other microbubble contrast agents, such as Sonazoid (GE Healthcare, Oslo, Norway), which consists of perfluorobutane-filled microbubbles and presently has marketing approval in Japan, Korea, China, and Norway, and Levovist (now off the market), which consists of air-filled microbubbles, have a postvascular hepatospecific phase 2–5 minutes after intravenous injection (7). In particular, Sonazoid enables very stable Kupffer phase imaging for at least 60 minutes, which yields high sensitivity in the detection of hepatocellular carcinoma (HCC) (9,10).

## CE US Technique

Microbubbles are injected through an intravenous line, preferably with a 20-gauge catheter to avoid microbubble destruction due to the Venturi effect and via an antecubital vein in the left arm. Microbubble bolus injection should be followed by a 5–10-mL saline flush at a rate of about 2 mL/sec to clear the intravenous line (7). In accordance with the US equipment manufacturer recommendations, low-acoustic-power contrast-specific modes with a mechanical index of 0.08–0.12 should be used. Low-acoustic-power B-mode imaging without contrast-specific modes is not feasible due to low image quality. It is crucial that a timer be started at the beginning of the saline flush to coincide with the actual injection of microbubbles. Dual-screen imaging with a separate contrast mode and B-mode images are helpful to guide the examination and determine the location of the nodule.

The arterial phase begins 10–20 seconds after injection and ends 30–45 seconds after injection (4). The portal venous phase begins after the arterial phase and lasts until 120 seconds after injection. The late phase lasts until microbubbles disappear (4–6 minutes after injection). CE US should be performed continuously during the arterial phase and intermittently during the portal venous and late phases. Intermittent imaging and use of a low frame rate and high signal persistence settings are important to minimize microbubble destruction and have adequate late-phase enhancement in the liver parenchyma. Since low frame rate decreases microbubble destruction, arterial phase enhancement is better visualized. On the other hand, the use of a high frame rate could show contrast material washout more clearly. Intermittent imaging at 30–60-second intervals should be performed until there is unequivocal clearance of microbubbles from the circulation at about 4–6 minutes after contrast material injection, even with a nonhepatospecific microbubble contrast agent, to better characterize washout that is often late in onset and mild in degree in HCCs. After the initial CE US scan, further microbubble injections may focus on the original nodule or on additional nodules, as required. If the arterial phase is missed due to small lesion size, difficult lesion location, or the patient being unable to hold his or her breath, and if there is evidence of an indeterminate nodule in the portal venous phase, a second microbubble injection can be made that focuses on the area of washout. In each case, microbubble injection should be repeated after complete microbubble disappearance (range, 7–10 minutes after previous injection).

## CE US Indications and Limitations

According to the European Federation of Societies for Ultrasound in Medicine and Biology and the World Federation for Ultrasound in Medicine and Biology, CE US is indicated to characterize all lesions found at surveillance or routine US in the cirrhotic or noncirrhotic liver to establish a diagnosis of HCC (followed by CT and MRI for staging), to characterize those nodules (especially if not suitable for biopsy) that remained indeterminate after CT or MRI, to select a nodule or nodules for biopsy when there are multiple nodules with different contrast enhancement patterns, and in patients with inconclusive cytologic or histologic results (4). The

main additional benefit for CE US is when CT or MRI *(a)* shows contrast material washout in the portal venous or late phase but does not show arterial phase enhancement or *(b)* shows arterial phase enhancement but does not show contrast material washout. CE US can provide the additional information presumably because of the intravascular nature of microbubble contrast agents and the continuity of acquisition, allowing continuous evaluation for 5 minutes (11). Moreover, CE US is recommended by the European Federation of Societies for Ultrasound in Medicine and Biology and the World Federation for Ultrasound in Medicine and Biology to characterize arterial phase hyperenhancement findings for observations in which mistiming is suspected with prior CT or MRI (11), to guide biopsy or treatment of focal liver lesions that are difficult to visualize on unenhanced US images, to improve visibility of the most appropriate nodules for biopsy, to monitor changes in enhancement pattern over time for selected hepatocellular nodules, to differentiate tumor in vein from bland thrombus based on contrast enhancement (12), and to monitor and target ablation therapy to treat HCC (13) during and after ablation therapy (4).

CE US is also endorsed by the Italian Association for Study of the Liver (14), the Japanese Society of Hepatology (15), and the Asian Pacific Association for the Study of the Liver (16). However, other major scientific societies, including the American Association for the Study of Liver Disease (17) and the European Association for the Study of the Liver (18), do not recommend use of CE US in hepatocellular nodule characterization because of the possibility that HCC will be misdiagnosed as intrahepatic cholangiocarcinoma (ICC) (19).

The use of CE US does not improve the ability to detect small HCC tumors. CE US is accurate in hepatocellular nodule characterization but is limited in hepatocellular nodule detection, especially if nodules cannot be detected with conventional US (4). CE US shares some common limitations with gray-scale US, in particular, inaccessibility of subdiaphragmatic or deep lesions, limited penetration in patients with large body habitus, and signal attenuation in patients with severe hepatic steatosis, while infrequent interference of bowel or gastric gas may also limit the success of CE US. Nodules located deeper than 10 cm from the skin surface because of excess subcutaneous or hepatic fat are not well depicted with CE US because of sound beam attenuation (20). In particular, the upper right subdiaphragmatic regions of the liver cannot be visualized in some patients through an acoustic window, and if a nodule cannot be seen with gray-scale US because of its location, CE US will not be useful. However, those nodules that are not detectable with gray-scale US may become visible by using some anatomic landmarks or contrast material washout in the late phase after microbubble injection or even by fusing CT or MRI with US. Nodule diameter smaller than 10 mm, very coarse heterogeneous cirrhotic liver, and poorly cooperating patients are further limitations of CE US.

## CE US LI-RADS Criteria: Major Imaging Features

LI-RADS criteria for CT and MRI were proposed to standardize the performance of liver imaging and the interpretation and reporting of results, to assist radiologists in the categorization of liver imaging findings in patients at risk for HCC, and to improve communication between radiologists and clinicians through the use of a common terminology (21). Generally, LI-RADS applies to a patient population at risk for HCC, which corresponds to patients with liver cirrhosis, chronic hepatitis B virus infection without cirrhosis, or current or prior HCC, and includes adult candidates for liver transplantation and adult liver transplant recipients (22). LI-RADS does not apply to children, nor does it apply to patients with vascular liver disorders or cirrhosis due to congenital hepatic fibrosis (21). In April 2014, the American College of Radiology (ACR) convened a working group of international experts to develop the CE US LI-RADS. The CE US LI-RADS was added to the ACR LI-RADS in 2016 (CEUS LI-RADS, version 2016) and September 2017 (CEUS LI-RADS, version 2017) as a standardized system for technique, interpretation, reporting, and data collection in patients at risk for HCC (22,23). The current version of CE US LI-RADS applies to pure blood pool agents, such as Lumason and Definity, but not to combined blood pool–Kupffer cell agents, such as Sonazoid (22). This is because blood pool agents provide effective arterial phase hyperenhancement and ensure pure contrast agent washout from malignant nodules.

Most newly discovered hyperenhancing nodules detected at CE US during HCC surveillance are HCC regardless of washout if the nodules do not show the typical appearance of hemangioma (24); however, 70%–90% of arterial phase–enhancing foci smaller than 2 cm without contrast material washout at CT or MRI are not HCCs (25). The specificity and sensitivity of CE US in the diagnosis of HCC in nodules smaller than 2 cm in a cirrhotic liver were found to be as high as 87% and 100%, respectively (24).

CE US LI-RADS could improve the integration of CE US into the multimodality approach for the study of the liver at risk for HCC, providing unique and complementary information to that obtained with CT and MRI (26). The assignment of a CE US LI-RADS category is based mainly on major imaging features corresponding to nodule size, presence or absence of arterial phase hyperenhancement, and nodule washout in the portal venous or late phase. Developed by experts in liver imaging, including radiologists, hepatologists, hepatopathologists, surgeons, and lexicon experts, and supported by the American College of Radiology, CE US LI-RADS includes every possible combination of nodule diameter, grade of arterial phase enhancement, and portal venous and late phase contrast agent washout to classify each observation according to distinct diagnostic categories that reflect the relative probability of benignity, HCC, or other malignancy (22,23,26). Any lesion that can be seen with gray-scale US can be scanned with CE US, although a nodule smaller than 1 cm identified at gray-scale US does not require immediate assessment with CT or MRI or CE US and can be followed up with unenhanced gray-scale US in 3 months. Most observations at CE US are true nodules, and the only exceptions are focal fatty infiltration and sparing.

*Nodule size* should be measured on unenhanced gray-scale US images in agreement with LI-RADS criteria for CT and

**Contrast-enhanced US LI-RADS Diagnostic Categories**

| Category | Criteria |
|---|---|
| LR-1 | Simple cyst, classic hemangioma, focal fatty change, or focal fatty sparing |
| LR-2 | Nodule size <10 mm, no AP enhancement, no washout, no additional enhancement patterns OR LI-RADS 3 observation stable for ≥2 years |
| LR-3 | Nodule size ≥10 mm, no AP enhancement, no washout, no additional enhancement patterns OR nodule size <10 mm, AP enhancement, no washout OR nodule size <20 mm, no AP hyperenhancement, and washout (≥60 seconds) |
| LR-4 | Nodule size ≥10 mm, AP hyperenhancement, no washout OR nodule size <10 mm, AP hyperenhancement, and washout OR nodule size ≥20 mm, no AP hyperenhancement, and washout (≥60 seconds) |
| LR-5 | Nodule size ≥10 mm, AP hyperenhancement, and washout |
| LR-M | Nodule of any size and washout (<60 sec) OR marked washout within 2 minutes OR rim enhancement and washout |
| LR-NC | Not categorizable due to image degradation or omission |
| LR-TIV | Tumor within the portal vein, hepatic vein, or both |

Note.—Arterial phase (AP) hyperenhancement is defined as diffuse enhancement with unequivocal nodule hypervascularity and no evidence of peripheral globular or rimlike enhancement. LI-RADS = Liver Imaging Reporting and Data System, LR-1 = definitely benign, LR-2 = probably benign, LR-3 = intermediate malignancy probability, LR-4 = probably hepatocellular carcinoma (HCC), LR-5 = definitely HCC, LR-NC = cannot be categorized due to image degradation, LR-TIV = tumor in vein, and LR-M = probably or definitely malignant but not HCC specific.

MRI (27). Nodule measurement after contrast material injection in the arterial phase could be biased by nodule diameter overestimation related to diffuse contrast enhancement blush involving both the nodule edges and the liver parenchyma due to adjacent liver tumoral infiltration and neoangiogenesis.

*Arterial phase hyperenhancement* (22,23,26) corresponds to nodule diffuse enhancement occurring from approximately 10–20 seconds after microbubble injection to approximately 30–45 seconds after microbubble injection. This enhancement is unequivocally greater than that of the background liver, and it is without any rimlike or peripheral discontinuous globular morphology. The observation of arterial phase hyperenhancement on CE US images in patients at risk for HCC represents a crucial finding, and this should lead to nodule classification as probable or even definite HCC diagnosis, although a hyperenhancing hemangioma or other benign hepatic lesions can also have this appearance. This is because CE US allows real-time evaluation of the enhancement of a nodule that is visible at gray-scale US, thereby enabling more sensitive detection of arterial phase hyperenhancement than CT or MRI, which may fail to demonstrate arterial phase hyperenhancement due to mistiming or limited contrast material resolution when compared with CE US (26). Moreover, CE US can show tumoral artery morphology in either the entire nodule or in only a portion of the nodule in the early arterial phase. Dysmorphic vessel morphology and centripetal filling of a nodule are both associated with HCC (5,28–30).

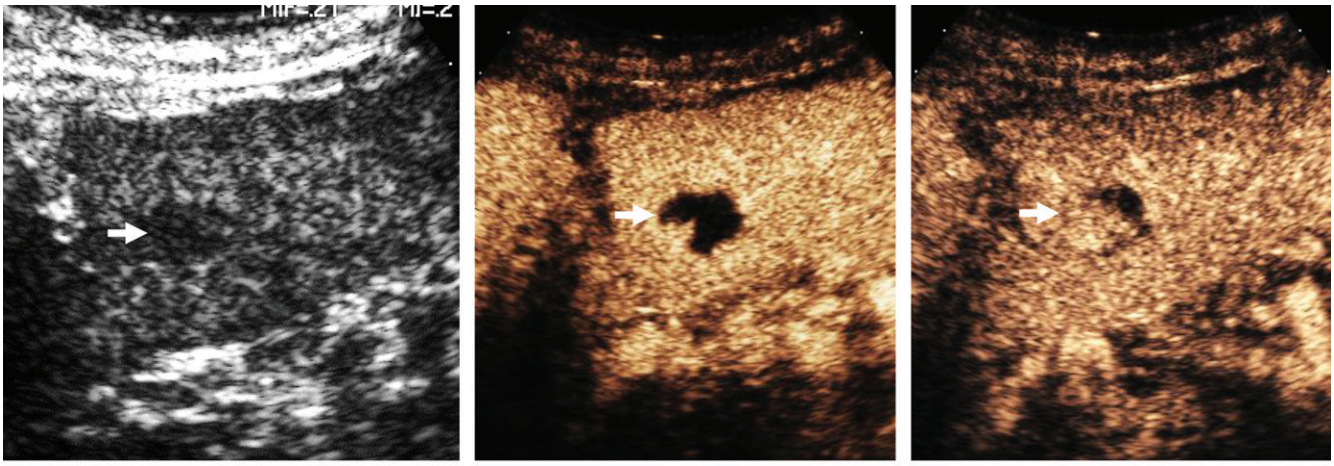
Arterial phase hyperenhancement could be seen in a wide variety of both benign and malignant focal liver observations, including a wide variety of liver masses and arterioportal shunts at CT, MRI, and CE US. One of the main assumptions of CE US LI-RADS is that, unlike CT and MRI, arterioportal shunts are not visualized on either unenhanced or CE US images (22,23,26), and when an arterioportal shunt is suspected at CT or MRI, routine gray-scale US will not show any abnormality or nodule to correspond with the arterial phase hyperenhancement seen with CT or MRI. This is not necessarily the case since, occasionally, some nodule-shaped or focal fatty sparing–associated intrahepatic arterioportal shunts may be visualized in patients with cirrhosis on unenhanced gray-scale US images. These shunts may simulate hyperenhancing nodules even on CE US images after microbubble contrast agent injection and, therefore, cannot be differentiated from true hepatocellular hyperenhancing nodules (29).

*Contrast material washout* corresponds to the visually assessed temporal reduction in nodule enhancement, in whole or in part, relative to the adjacent liver beginning in or after the arterial phase and resulting in portal venous or late phase hypoenhancement. On CE US images, all malignant lesions, including HCC, ICC, and metastases, show contrast material washout. Hepatocellular adenoma can also show contrast material washout (31); however, this histotype is not found in patients with liver cirrhosis or chronic hepatitis.

## CE US LI-RADS Diagnostic Categories and Management

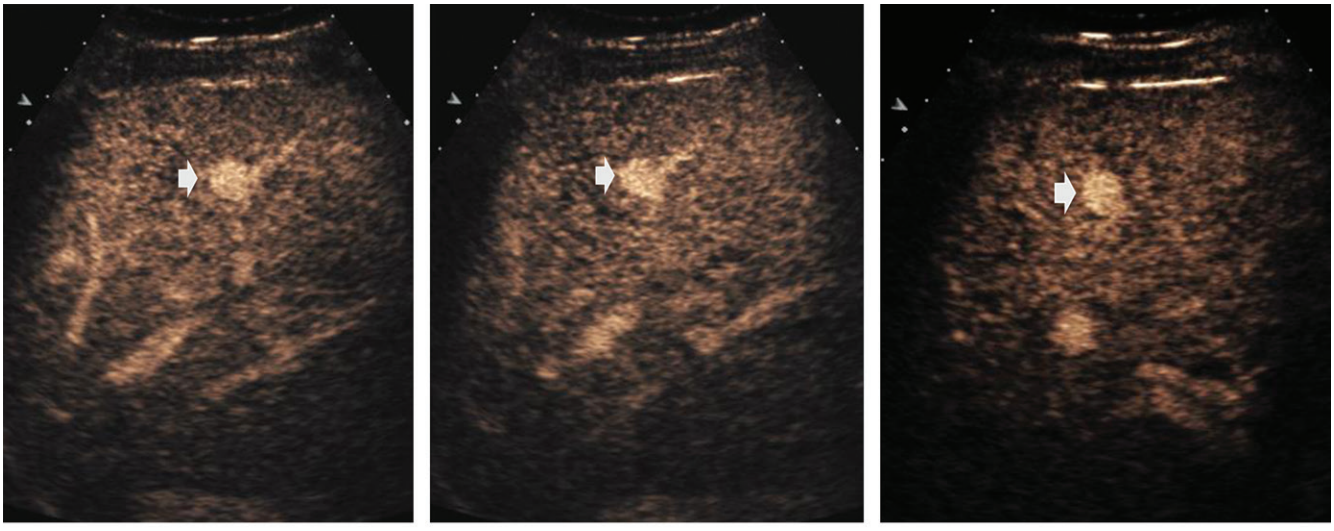
CE US LI-RADS includes five fundamental diagnostic categories (Table): LR-1 (definitely benign), LR-2 (probably benign), LR-3 (intermediate malignancy probability), LR-4 (probably HCC), and LR-5 (definitely HCC). Moreover, LR-NC (not categorized due to image degradation), LR-TIV (tumor in vein), and LR-M (probably or definitely malignant but not HCC specific) diagnostic categories are also included. Unlike LI-RADS for CT and LI-RADS for MRI, therapy monitoring in the treatment of HCC is not presently addressed in the current version of CE US LI-RADS.

CE US LR-1 (Fig 1) includes focal hepatic lesions that are definitely benign on CE US images due to globular peripheral enhancement followed by variable fill-in in hemangiomas (including fast-filling hemangiomas). It also includes lesions that appear isoenhanced when compared with the adjacent liver parenchyma on arterial and portal venous phase CE US images, with no evidence of contrast material washout in echogenic non-masslike and nonspherical observations on gray-scale



a. b. c.

**Figure 1:** Images of contrast-enhanced (CE) US LR-1, hemangioma with fill-in, in a 65-year-old woman with chronic hepatitis B virus infection and a nodule at surveillance US. **(a)** Gray-scale US image shows a right lobe hypoechoic focal liver nodule (arrow). **(b, c)** Sequential arterial phase CE US images obtained 23 seconds (**b**) and 40 seconds (**c**) after microbubble injection show peripheral nodular enhancement with progressive and almost complete fill-in (arrow).



a. b. c.

**Figure 2:** Images of contrast-enhanced (CE) US LR-2, probably benign nodule, in a 27-year-old man with cryptogenic cirrhosis. **(a)** Arterial phase CE US image obtained after microbubble injection shows hyperenhancement (arrow) in a 10-mm-diameter nodule close to a portal vessel. **(b, c)** US images obtained 50 seconds (**b**) and 75 seconds (**c**) after microbubble injection show the nodule (arrow) remains hyperenhanced in comparison with the adjacent hepatic parenchyma, without any evidence of washout. Short interval surveillance has continued to show interval stability for more than 1 year, suggesting a diagnosis of rapid-filling hemangioma.

unenhanced US images corresponding to focal fatty change and focal fatty sparing. Unenhanced lesions in all phases corresponding to simple cysts or intrahepatic hematomas are also included.

CE US LR-2 (Fig 2) generally corresponds to typical regenerative nodules—masslike or nodular lesions that appear isoenhanced when compared with the adjacent liver parenchyma in all phases—or to any observation previously categorized as CE US LR-3 with interval size stability for at least 2 years. Patients with an observation classified as CE US LR-1 or LR-2 may return to regular 6-month surveillance.

CE US LR-3 nodules (Fig 3) have an intermediate malignancy probability. They include nodules in a variety of sizes and with absence of either arterial phase hyperenhancement or late and mild contrast material washout (Table). Nodules classified as LR-3 generally require alternative imaging or follow-up. Biopsy may be required in select cases based on multidisciplinary discussion (23,26).

CE US LR-4 nodules (Fig 4) are lesions that are probably HCCs but that cannot be diagnosed with absolute certainty. They are highly suspicious for HCC but lack the precise requirements for this diagnosis (Table). In a recent publication, Terzi et al (28) wrote that LR-4 observations corresponded to HCC nodules in 87% of cases and usually require biopsy. However, alternative imaging or short-term (<3 months) imaging follow-up can be applied if neither biopsy nor treatment is implemented immediately based on multidisciplinary discussion (23,26).

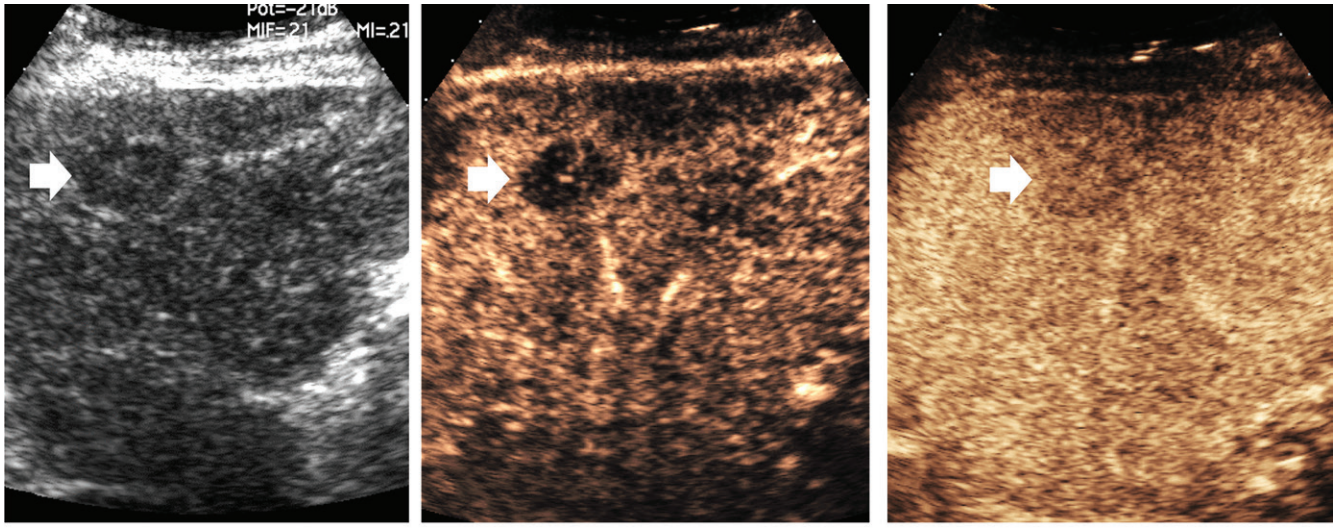



**Figure 3:** Images of contrast-enhanced (CE) US LR-3, indeterminate malignancy probability, in a 35-year-old man with hepatitis C–related cirrhosis. **(a)** Surveillance B-mode US image shows one 19-mm-diameter hypoechoic nodule (arrow). **(b, c)** CE US scans obtained with the Cadence system (Siemens, Erlangen, Germany) after microbubble injection. The nodule appears hypoenhancing (arrow) to the adjacent liver in the arterial phase (**b**). At 70 seconds after microbubble injection, the nodule (arrow) is isoenhancing to the adjacent liver in the portal venous phase (**c**). Subsequent biopsy revealed a macroregenerative nodule.

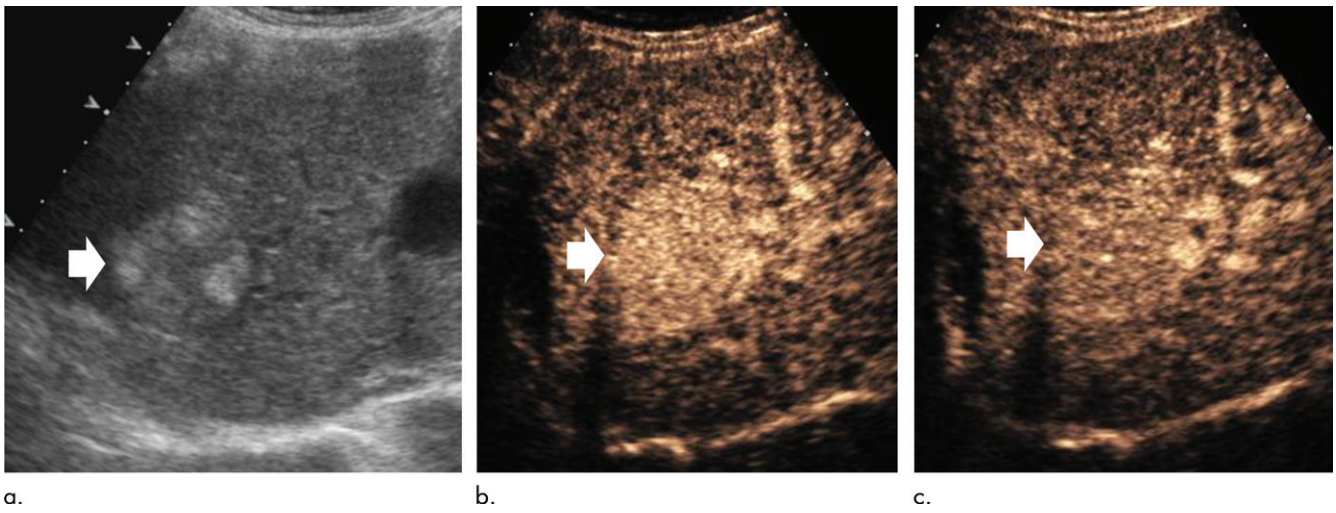



**Figure 4:** Images of contrast-enhanced (CE) US LR-4, probably hepatocellular carcinoma (HCC), in a 55-year-old woman with hepatitis C–related cirrhosis. **(a)** Surveillance US image shows one 25-mm-diameter hyperechoic nodule with a mosaic pattern (arrows). **(b)** US image obtained in the arterial phase shows that the nodule (arrow) is hyperenhanced in comparison with the adjacent liver. **(c)** US image obtained 140 seconds after microbubble injection shows the nodule (arrow) is slightly hyperenhanced in comparison with the adjacent liver, with incomplete contrast material washout. There is no evidence of contrast material washout. Subsequent biopsy was positive for well-differentiated HCC. Despite the evidence of a CE US Liver Imaging Reporting and Data System ancillary feature corresponding to evidence of mosaic pattern on unenhanced US, this does not allow an upgrade from CE US LR-4 to CE US LR-5.

CE US LR-5 (Fig 5) is HCC with nearly 100% probability; thus, confirmation with biopsy prior to treatment is unnecessary. CE US LR-5 is highly specific for HCC (29,30), enabling it to be used for confident noninvasive diagnosis, and practically abolishes the risk of misdiagnosis of other malignant entities (eg, ICC) for HCC, with a negligible reduction in sensitivity (5,29). Management of CE US LR-5 nodules may include local-regional therapy, surgical resection, or transplantation, without a need for tissue diagnosis. There are no differences in sensitivity between CE US, CT, and MRI in HCC nodule characterization (30,32). However, since CE US is unsuitable for HCC staging, CE CT or MRI is necessary for staging disease in the remaining liver once a malignant lesion (either HCC or another malignancy) is diagnosed (30). Some studies suggested that the wash-in patterns of ICC lesions at CE US were similar to those of HCC lesions in patients with liver cirrhosis or small tumor size (19,33). A combined HCC and ICC has an enhancement pattern similar to that of an ICC or HCC in comparable proportion at both CE US and CT (19,34).

Patients with CE US LR-TIV are usually referred for a multidisciplinary meeting for consensus management (30,35). The

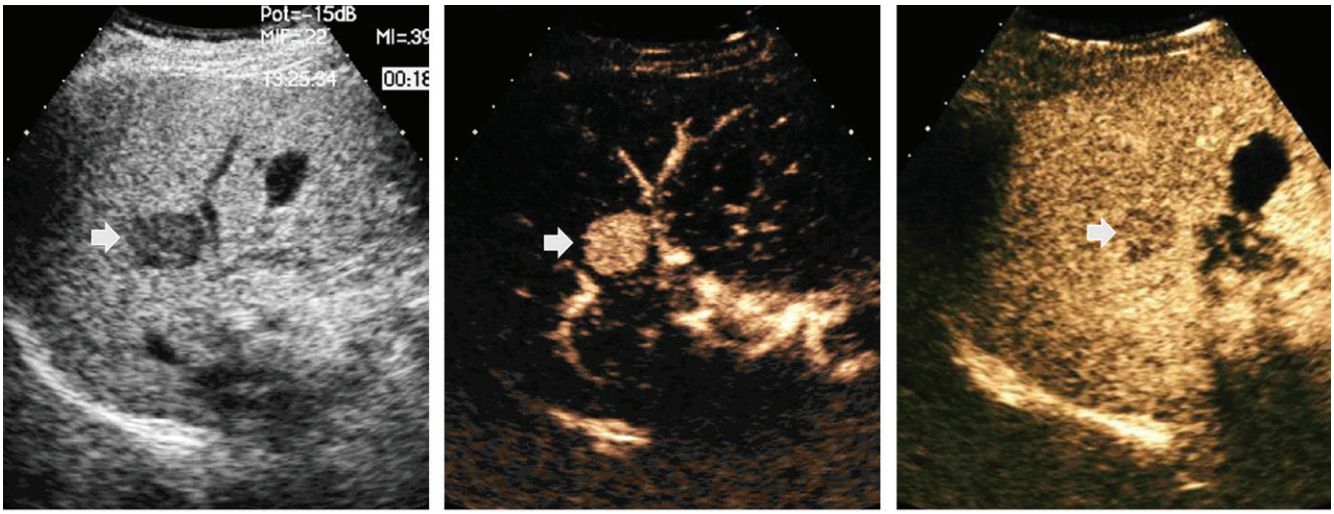



**Figure 5:** Images of contrast-enhanced (CE) US LR-5, definitely hepatocellular carcinoma (HCC), in a 45-year-old man with hepatitis C–related cirrhosis. **(a)** Surveillance US image shows one 20-mm-diameter hypoechoic nodule (arrow). **(b)** Arterial phase US image shows that the nodule (arrow) is hyperenhanced compared with the adjacent liver. **(c)** US image obtained 90 seconds after microbubble injection shows the nodule (arrow) with unequivocal contrast washout. After CE US, which was diagnostic for HCC nodule, the patient underwent CT for staging purposes. (Images courtesy of Professor Mirko D'Onofrio, University of Verona, Italy.)

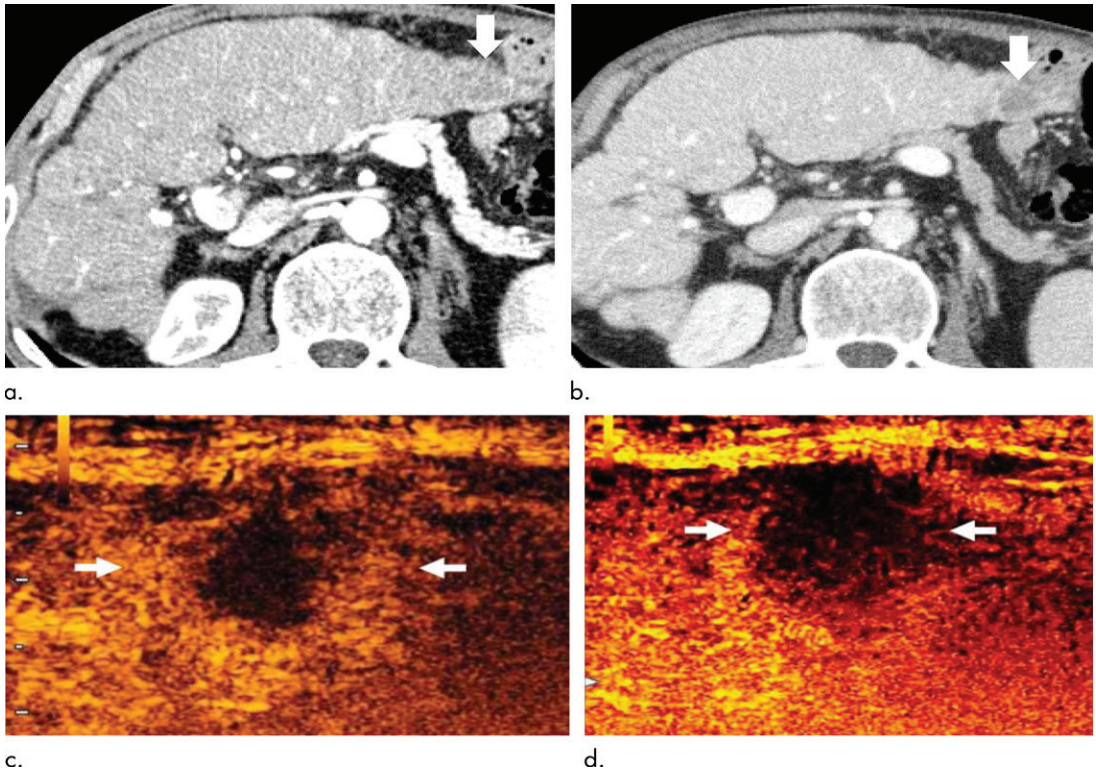



**Figure 6:** Images of contrast-enhanced (CE) US LR-M, probably or definitely malignant nodule other than HCC, in a 78-year-old-man with hepatitis B virus infection and laryngeal cancer. A small growing nodule was seen with CT. **(a, b)** Contrast-enhanced CT images in the arterial (**a**) and portal venous (**b**) phases after iodinated contrast agent injection. The lesion (arrow) was considered indeterminate due to persistent hypoattenuating appearance. **(c)** Arterial phase CE US image obtained after microbubble contrast agent injection shows the mass has rimlike peripheral enhancement (arrows) surrounding the center of the lesion, which remains hypoechoic. **(d)** CE US image shows rapid microbubble contrast agent washout prior to 60 seconds, (shown at 34 seconds), with minimal microbubble persistence within the lesion (arrows). Biopsy after CE US revealed liver metastasis.

strength of CE US is in real-time direct visualization of arterial phase hyperenhancement in the tumor thrombus and morphologic ancillary features, which are easily distinguished from portal venous phase enhancement of a patent lumen and a persistently nonenhancing bland thrombus. CE US has high sensitivity in the detection and correct differentiation of a tumor thrombus from a bland thrombus (33,35). CE US LR-TIV should lead to alternative imaging assessment or repeat imaging, biopsy, or treatment.

CE US LR-M (Fig 6) includes malignant nodules other than HCC with a washout time earlier than 60 seconds (36–38) or with marked washout within 2 minutes after contrast material injection or peripheral rimlike enhancement followed by contrast material washout in the arterial phase (36–38). Peripheral rimlike hyperenhancement in the arterial phase has been reported in 38%–69% of ICCs (36–41). Increasing late phase enhancement of ICC seen with CT or MRI and due to interstitial leakage of iodinated or gadolinium-based contrast agents may be infrequently associated with misdiagnosis as a benign tumor, while marked contrast material washout seen with CE US corresponds to the typical appearance of malignancy. Thus, combining CE US with CT or MRI may be beneficial (30). Management of CE US LR-M nodules is variable and depends on the type of malignancy suspected. CE US LR-M observation should lead to surgical resection or even ablation and chemoembolization. However, biopsy is frequently needed for a CE US LR-M observation, as there is a lack of diagnostic imaging specificity. ICC, hepatocholangiocarcinoma, and metastases account for most tumors characterized as CE US LR-M.

Since differentiation between typical hepatocellular lesions (CE US LR-3, LR-4, and LR-5) and malignant tumors with enhancement characteristics not specific for HCC (CE US LR-M) with CE US relies on onset after microbubble injection and the degree of washout, initial real-time imaging with dynamic digital cine-clip acquisition 30–45 seconds after microbubble injection and stopping and resuming insonation in the portal venous and late phases are recommended. For these reasons, it is crucial to start the timer on the US screen at the beginning of the saline flush (23). When initial washout onset is detected at or after 60 seconds, it is characterized as late onset and considered diagnostic for HCC.

The degree of nodule washout is assessed by comparing the degree of contrast enhancement of the nodule relative to the surrounding liver. Marked washout is diagnosed when there is a small amount of contrast material within the mass but a large difference regarding the adjacent liver within 2 minutes after contrast material injection in the periphery and central region. Marked washout is suggestive of a probable categorization as LR-M since HCC usually keeps microbubbles, even when the liver nodule becomes less enhanced than the surrounding liver but still demonstrates some degree of persistent contrast enhancement.

## CE US LIRADS Criteria: Ancillary Features

Although ancillary features are simpler and less numerous in CE US LI-RADS than in CT LI-RADS or MRI LI-RADS, they are still very important. Ancillary features (definite interval size increase, mosaic appearance of the nodule, nodule-in-nodule architecture on arterial phase) may be applied to diagnostic accuracy and confidence in HCC characterization or to adjust CE US LI-RADS categories and are classified as favoring malignancy in general, HCC in particular, or benignity. Ancillary features favoring HCC include a mosaic appearance of the nodule, a nodule-in-nodule appearance in the arterial phase after microbubble injection, and a definite interval size increase (>50% diameter increase in 6 months) (30). On completion of the algorithm categorization, ancillary features may be used at the interpreter's discretion to increase diagnostic confidence or to adjust a LI-RADS category. Ancillary features may be used to upgrade by a maximum of one category up to CE US LR-4 but cannot be used to adjust the score to CE US LR-5 (Fig 4). Ancillary features are crucial to upgrade from CE US LR-3 to CE US LR-4.

## Potential Limitations and Pitfalls of the CE US LI-RADS Algorithm

Although CE US has been used to characterize liver lesions and for other indications for many years worldwide, it is fairly new in the United States. CE US LI-RADS criteria were developed in the United States, where HCC histology, epidemiology, and imaging features are different from those in Europe and Asia (42). Consequently, multicenter prospective studies are needed to validate CE US LI-RADS criteria. In China, hepatitis B virus infection is the major cause of HCC, whereas in Japan, the United States, and Europe, hepatitis C virus infection is predominant. Soon, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis will be the leading contributors to HCC in Europe and the United States (42).

Although the diagnostic accuracy of LR-4 and LR-5 categories for HCC nodule characterization was recently found to be 86%–98% (28,43), the LR-3 category encompasses an excessively high number of observations with many different combinations of size and enhancement patterns and, consequently, an excessively high number of HCC nodules (range, 47%–50%) (28,43). This limits the overall diagnostic category of CE US LI-RADS in its present form. For these reasons, a variant of the original CE US LI-RADS, named LI-RADS CE US, has been published in Europe (44). This algorithm includes four basic diagnostic categories instead of five, as in the original CE US LI-RADS (with the indeterminate category of LR-3 omitted from LI-RADS CE US). Some other variants of CE US LI-RADS were proposed, including Erlanger Synopsis of Contrast-Enhanced Ultrasound for Liver Lesion Assessment in Patients at Risk, or ESCULAP, (45) using even subtotal infiltration of a liver lobe as an additional feature of HCC.

A possible solution to reduce the number of observations included in CE US LR-3 could be to upgrade nodules smaller than 2 cm in diameter without hyperenhancement in the arterial phase and with washout in the late phase (which mostly correspond to HCCs) from CE US LR-3 to CE US LR-4 and to downgrade nodules of any size with arterial phase hypoenhancement and without any evidence of late phase washout or that appear isoenhanced on late phase images (which mostly correspond to macroregenerative nodules) from CE US LR-3 to CE US LR-2. Hepatocellular nodules 2 cm in diameter or smaller with arterial phase hyperenhancement followed by isoenhancement in the

portal venous and late phases remain equivocal since they can represent well-differentiated HCCs or hyperenhancing benign nodules (46). The persistent microbubble uptake in the portal venous and late phases that can be observed in malignant nodules (eg, well-differentiated HCC with mild washout) is probably due to the similarity of microbubble kinetic distribution and pooling in tumoral nodules and adjacent liver parenchyma sinusoids (45–47). There is an overall concordance between CE US and CT in depicting arterial phase hyperenhancement in 44% of HCCs 2 cm or smaller (48). The combined assessment of CE US and CT could reduce the number of false-negative findings in HCCs 2 cm or smaller since the combination of CE US and CT in depicting unequivocal arterial phase hyperenhancement, portal venous phase hypoenhancement, or both could improve HCC characterization if compared with separate techniques (48).

Besides the excessively large diagnostic category of LR-3 observations, there are further limitations of the CE US LI-RADS algorithm in its present form. Nodules smaller than 10 mm with hyperenhancement in the arterial phase and washout in the late phase should be upgraded from CE US LR-4 to CE US LR-5. Operator experience could have a relevant influence on CE US LI-RADS classification in patients at risk for HCC. CE US allows real-time scanning of hepatocellular nodules with the possibility of prolonged liver insonation. This has been achieved as a result of the safe profile and stability of microbubbles persisting in the bloodstream for several minutes. The operator must identify the most suitable acoustic window to evaluate the lesion and observe tumor enhancement after microbubble injection, without moving the transducer from its initial position. Correct image interpretation is less straightforward and depends on reader experience. Theoretically, CE US could be less observer dependent than CT or MRI due to its better temporal resolution and since the field of view is more concentrated on the focal liver lesion; however, it remains dependent on operator and observer experience (49). To overcome these limitations, operator training should be focused on both technical skills and image interpretation. Although visual analysis is the simplest method to analyze liver tumor enhancement, if it is compared with quantitative analysis it is often penalized by the fact that the eyes of the observer tend to focus on a specific portion of the enhancing tumor instead of comparing the echogenicity of the whole tumor with that of the adjacent liver in a more global and reproducible manner. Interreader agreement in assessing the degree of hepatic lesion hyperenhancement in the arterial phase after microbubble contrast agent injection is higher than that for contrast material washout during the portal venous or late phase (49) because perception of microbubble contrast agent washout compared with adjacent enhancing liver parenchyma varies between observers (50,51). In particular, nodule washout could be equivocal in some HCC nodules, and determination of the presence or absence of mild contrast material washout is often influenced by observer experience (49). Since the evidence of contrast material washout is crucial for HCC diagnosis, diagnosis by different observers could create disagreement and result in HCC misclassification.

Different US equipment technology could also represent a further limitation of the CE US LI-RADS algorithm. Although it is likely that CE US LI-RADS can be extrapolated to all US systems, there is an influence of US equipment and transducer sensitivity to microbubble contrast agent signal (52) that is mainly related to the employed electronics, screen brightness, and contrast-specific mode. In particular, image brightness from different US equipment, variability in the acoustic power output of US machines, and the compression algorithm used to represent the wide range of echo signal intensities on screen and specific for each US system could influence nodule appearance after microbubble injection and evidence or absence of washout. The insonation technique itself (timing, signal persistence, insonation power, etc) and the number of seconds of insonation and image frame rate may have a strong influence on washout timing in patients with HCC. While real-time imaging is crucial to assess arterial phase hyperenhancement, the use of continuous scanning after 60 seconds will result in increased microbubble destruction in both the nodule and the adjacent liver, with limited visibility of contrast material washout. For this reason, prolonged intermittent scanning is crucial to detect late and mild nodule washout, which is one of the major diagnostic features for HCC diagnosis. In some HCC nodules, mild washout can be very delayed (even later than 5 minutes), especially in well-differentiated HCC nodules (53), and it can be detected only with high-resolution equipment and intermittent imaging with minimal microbubble destruction in the late phase.

Even LR-M criteria should be revised. Since differentiation between hepatocellular lesions typical for HCC (LR-4 and LR-5) and malignant tumors with enhancement characteristics different from HCC (LR-M) relies on the onset of washout (before or after 60 seconds), the evidence of early washout in an hyperenhancing nodule in the arterial phase does not necessarily enable one to rule out HCC, since washout may occur earlier than 60 seconds in poorly differentiated HCCs (53). However, peripheral rimlike enhancement, early washout, and marked washout identified in 65%, 92%, and 61% of ICC nodules, respectively, were found to be the most useful CE US features for ICC diagnosis (54). Unfortunately, the overall accuracy of LR-M in nodules 2 cm or smaller was as low as 11% (43). These issues should suggest a revision of LR-M criteria. Most likely, the time criterion for the onset of contrast material washout should be reduced to less than 60 seconds. In addition, marked washout within 2 minutes should be shifted to 3–4 minutes, and marked washout within 2 minutes should be considered typical of HCCs to increase specificity while arterial phase peripheral rimlike enhancement should be maintained as the more specific criterion for LR-M (36–40).

## Conclusion

The contrast-enhanced (CE) US Liver Imaging Reporting and Data System is a reference algorithm used to produce a structured report for hepatocellular carcinoma (HCC) diagnosis and to improve communication between radiologists and clinicians. However, some limitations should be considered, including US equipment variability in sensitivity to microbubble contrast agents, grade of observer experience in CE US, an excessively high number of HCC nodules classified as intermediate malignancy observations, and the wide temporal contrast

material washout cutoff (<60 seconds), which makes it difficult to differentiate HCC nodules from other malignancies.

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