Key Dates

- April 2014: ACR CEUS LI-RADS working group was formed
  - Chair: Yuko Kono, Co-chair: Andrej Lyshchik
  - Members: David Cosgrove, Christoph Dietrich, Hyun-Jung Jang, Tae Kim, Fabio Piscaglia, Claude Sirlin, Juergen Willmann, Stephanie Wilson
  - Ex-officio members: Cynthia Santillan, Avinash Kambadakone, Donald Mitchell
  - Member in Training: Alexander Vezeridis
- Beta versions of the CEUS LI-RADS algorithm presentations
  - 11/14/15-11/17/15 ROMA 25SIUMB CONGRESSO NAZIONALE XXIX GIORNATE INTERNAZIONALI DI ULTRASONOLOGIA.
    La nuova classificazione CEUS Li-RADS americanaper i noduli su cirrosiF. Piscaglia (Bologna) – Fabio Piscaglia et al.
  - 11/29/15-12/04/2016 RSNA 2015 Educational Exhibit
    Incorporation of CEUS Into LI-RADS for Diagnosis of Hepatocellular Carcinoma (HCC): A Work in Progress – Hyun-Jung Jang et al.
  - 03/19/2016 AIUM 2016 Oral Presentation
    Contrast-Enhanced Ultrasound Liver Imaging Reporting and Data Systems (CEUS LI-RADS) Yuko Kono/Stephanie Wilson et al.
  - 03/16-03-21/2016 AIUM 2016 Poster 2378960
    Contrast-Enhanced Ultrasound Liver Imaging Reporting and Data System for Diagnosis of Hepatocellular Carcinoma: Initial Proposal – Yuko Kono et al.
  - 9/9/15 ICUS annual meeting
    Li-RADS Liver Reporting and Diagnosis Systems CEUS Initiative - David Cosgrove et al.
- May 21 2016: Final CEUS LI-RADS v2016 algorithm v2016 submitted to Steering Committee
- June 24, 2016: The algorithm was officially approved by the ACR LI-RADS Steering Committee
- June 24, 2016: The algorithm was submitted to the ACR for public release

LI-RADS v2016

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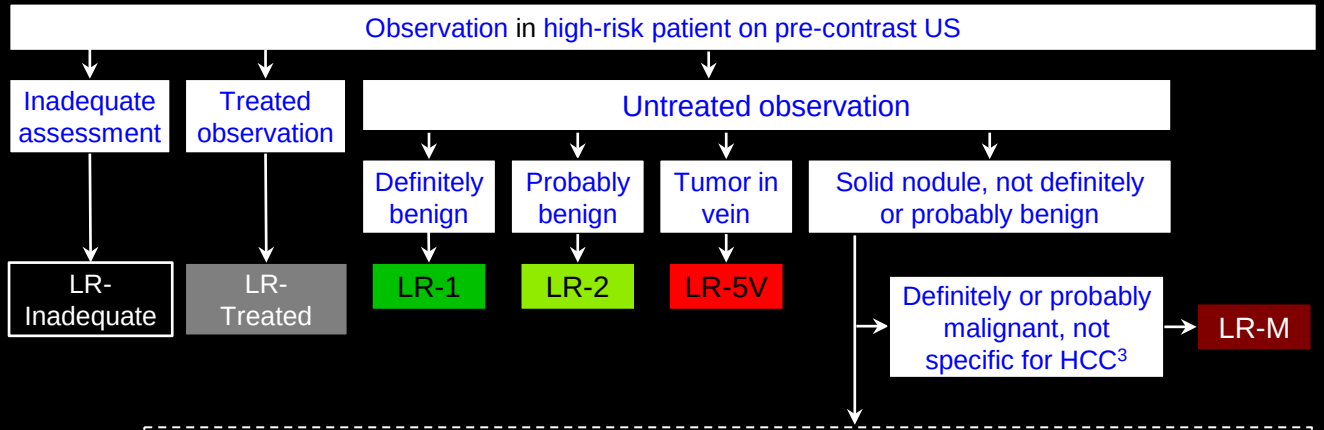
CEUS LI-RADS

v2016

Algorithm for CEUS



	Arterial phase hypo/isoenhancement		Arterial phase hyperenhancement[1]	
Dimension (mm)	< 20	≥ 20	< 10	≥ 10
No washout of any type	LR-3	LR-3	LR-3	LR-4
Late and mild washout[2]	LR-3	LR-4	LR-4	LR-5

Apply ancillary features and then apply tie-breaking rules to adjust category as appropriate

[1] Arterial phase hyperenhancement: whole or in part, not rim or peripheral discontinuous globular enhancement
[2] Late in onset (≥ 60 seconds) and mild in degree: in whole or in part, with no part showing early or marked washout
[3] Early onset washout (<60seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

LR-1

- Cyst
- Classic hemangioma
- Definite focal hepatic fat deposition or sparing

LR-2

- Isoenhancement in all phases
  - Distinct solid nodule <10mm OR
  - Not a distinct solid nodule, any dimension
- Observation previously LR-3, and stable dimension for 2 years or more

LR-5V

- Definite enhancing soft tissue in vein regardless of visualization of parenchymal mass/nodule

LR-M

Washout Characteristics:
- Early onset washout (< 60sec) and/or marked (punched out) appearance

Arterial phase enhancement
- Rim enhancement

Acknowledgments

Feedback? Email RADS@acr.org

General Indications for CEUS

- CEUS is performed to characterize observations detected at surveillance US
- CEUS can be performed to characterize observations detected on prior CT / MRI if the observations are visible as distinct nodules on pre-contrast gray-scale ultrasound
- In select cases, CEUS examiners, at their discretion, can perform CEUS to characterize nodules occult on pre-contrast gray-scale ultrasound using anatomical landmarks, image fusion or repeat contrast injections. Such characterization requires substantial experience and expertise. It is outside the purview of CEUS LIRADS v2016 and v2017, but may be addressed in CEUS LIRADS v2020

LI-RADS v2016

Specific Indications for CEUS

- 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
- To characterize observations categorized LR-3, LR-4, or LR-M on either CECT or CEMRI
- To characterize biopsied observations with inconclusive histology
- To contribute to the selection of observation(s) for biopsy when they are multiple or have different contrast patterns
- To monitor changes in enhancement pattern over time when a nodule under surveillance is not diagnostic for HCC
- To differentiate bland thrombus from tumor in vein (“tumor thrombus”)
- To assess treatment response

NOTE: The Guidelines from The World Federation for Ultrasound in Medicine and Biology (WFUMB) incorporate the combined input of CEUS experts from multiple international US societies and encourage the selection of CEUS for many indications in the characterization of nodules in a cirrhotic liver[1]. Today, CEUS is an important component of many international guidelines, including nations with a high prevalence of HCC (Japan, Canada, and Europe). It is not currently a part of AASLD guidelines, because of theoretical concerns for misdiagnosing intrahepatic cholangiocarcinoma (ICC) for HCC when CEUS is used alone (1%-2%)

References:

1. Claudon M, Dietrich CF, Choi BI, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver--update 2012: a WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. Ultraschall Med 2013;34:11-29. Ultrasound Med Biol 2013;39:187-210.

CEUS LI-RADS Technical Recommendations

Timing

1) Pre-contrast imaging:

- Used to identify the observation/nodule and select the appropriate acoustic window for CEUS
- Imaging in the longitudinal plane is helpful to minimize out-of-plane motion of the observation/nodule with respiration

2) Contrast-enhanced imaging:

- The dual blood supply of the liver from the hepatic artery (25%–30%) and the portal vein (70%–75%) gives rise to three overlapping vascular phases on CEUS study
- The *hepatic arterial phase* provides information on the degree and pattern of the arterial vascular supply. It generally starts within 20 seconds after injection and lasts for an additional 10-25 seconds, depending on the individual patient's circulatory status. This phase may be of short duration and the temporal enhancement pattern may evolve rapidly, sometimes within seconds. Real-time imaging with high frame rate and storage of cinematic images is needed to ensure optimal timing of the arterial phase and to capture the rapidly evolving arterial enhancement features. Slow-motion replay of stored cine loop is often helpful
- The *portal venous phase* begins around 30 to 40 seconds and conventionally lasts until 2 minutes after injection
- The *late phase* lasts until the clearance of the ultrasound contrast agent from the circulation and is limited to 4–6 minutes with available agents
- The time after injection at which washout is first detected (i.e., at which the observation first becomes unequivocally hypoechoic relative to liver) must be recorded precisely, if possible to the nearest second. Rationale: the time of washout onset is needed to differentiate HCC from potential other malignancy. As described further in slides 35&36, washout onset before 60 seconds suggests non-hepatocellular tumor whereas washout onset after 60 seconds may suggest either hepatocellular or non-hepatocellular tumor depending on the degree of washout and other features

Available Contrast Agents

- FDA approved for liver imaging:
  - Lumason/SonoVue (Sulfur hexafluoride lipid-type A microspheres, Bracco Diagnostics Inc. Marketed as Lumason in the USA and as SonoVue outside the USA)

- Agents for off-label use in the USA
  - Definity (Perflutren Lipid Microsphere, Lantheus Medical Imaging, Inc.)
  - Optison (Perflutren Protein-Type A Microspheres Injectable Suspension, GE Healthcare) (currently, documentation of successful use for liver imaging is lacking)

The current version of CEUS LI-RADS is based on use of purely intravascular contrast agents listed above. Use of the newer contrast agent Sonazoid (perfluorobutane within a phosphatidyl serine shell, GE Healthcare, Oslo) currently limited to Japan, South Korea and Norway where this agent is approved for clinical use. This agent demonstrates prolonged liver uptake due to active phagocytosis by Kupffer cells and might significantly improve diagnostic accuracy of CEUS. Its use will be integrated into CEUS LI-RADS v2020

Injection Technique

- Contrast injection should be performed through an IV line, preferably no smaller than 20G, to avoid bubble destruction
- Injection through central venous lines and infusion ports is acceptable as long as all safety and aseptic requirements are met. Note – use of the central venous lines and infusion ports will shorten the contrast arrival time
- Contrast bolus should be delivered over 2-3 seconds. Care should be taken to prevent increase in contrast syringe pressure, since this can destroy the bubbles within the syringe, leading to reduced enhancement and impaired image quality. Use of a 1mL syringe and extension tubing is preferred for Definity contrast administration. Use of the supplied 5mL syringe is preferred for Lumason/SonoVue
- The bolus of contrast should be immediately followed by a 5-10 mL normal saline flush delivered at the rate of approximately 2 mL/sec
- The scanner’s electronic timer should be started at the end of contrast injection (immediately prior to or simultaneous with onset of flush)

Suggested Imaging Parameters

- Low mechanical index (MI) contrast agent-specific imaging modes should be used. Users should refer to the ultrasound scanner manufacturer manuals and, if needed, obtain additional technical support from the manufacturers, to ensure proper system settings before undertaking CEUS studies
- Dual screen imaging with separate contrast mode and B-mode imaging is helpful to guide the exam
- Availability of simultaneous caliper display on both screens is ideal for observation/nodule localization
- Arterial phase and beginning of portal phase (up to 60 sec after the contrast injection) should be performed continuously and without interruption
- After 1 minute post injection, imaging can be performed using intermittent scanning to minimize microbubble destruction
- The exam should be continued until near complete clearance of the contrast agent (usually 5-7 min after the injection) to better characterize washout that is late in onset and mild in degree

Potential Pitfalls and Challenges

- Observation/nodule dimension less than 10mm
- Subdiaphragmatic or deep location
- Large body habitus
- Hepatic steatosis
- Very coarse heterogeneous cirrhotic liver
- Poorly cooperating patients
- Interfering bowel or gastric gas
- Nonlinear propagation artifact, a CEUS phenomenon, is associated with pseudo-enhancement following microbubble contrast injection. It is caused by the nonlinear propagation of sound through intervening microbubble-perfused tissue and is, therefore, most marked deep in the field of view

Advantages of CEUS

Real Time Imaging: Images are acquired at 10-30 frames/second in the arterial and portal venous phases

- high-temporal resolution assessment of targeted observations
- high temporal-resolution assessment of arterial phase hyperenhancement and washout
- permits assessment of rapid changes in enhancement and/or washout that could be missed with lower temporal resolution
- injections may be repeated, allowing assessment of enhancement patterns from different angles or using different parameters to increase diagnostic confidence may improve sensitivity for detecting transient APHE (arterial phase hyperenhacement) that could be missed with lower temporal resolution. CEUS can be a problem solving modality to detect APHE that may be missed at CT or MRI

High spatial resolution

- US provides higher in-plane spatial resolution than CT or MRI. This can help resolve anatomic and pathologic structures too small to be visible with CT or MRI and so may contribute to lesion detection and characterization

Hemangiomas:

- may permit detection of peripheral discontinuous globular enhancement that rapidly coalesce. This can help increase diagnostic confidence for hemangioma (LR 1)

PV thrombus:

- may help differentiate tumor vascular invasion (LR 5V) from bland thrombus

Limitations of CEUS

- Usually only one target observation can be categorized with one injection
- Usually only a few observations can be categorized in one exam
- CEUS generally not suitable for staging
- Images usually cannot be reformatted into different imaging planes
- Co-localization of CEUS and CT-/MRI-detected observations may be challenging

Differences between CEUS and CT/MRI LI-RADS

Almost all enhancing observations are nodules

- Enhancing observations at CEUS are almost always nodules
- Explanation: AP shunts do not manifest as enhancing pseudolesions at CEUS
- Implications:
  - vascular pseudolesions are rarely observed at CEUS and so do not cause diagnostic confusion
  - observations that enhance in AP and that fade to isoenhancement are arterialized nodules and are likely to be malignant. Hence these may be assigned a higher category at CEUS than at CT or MRI
  - CEUS LI-RADS frequently uses the term “nodule” rather than “observation”

Difference on pre contrast study visibility

- CEUS LI-RADS applies only to observation detected at pre-contrast ultrasound
- CT/MRI LI-RADS apply to any observation even if not seen on pre-contrast scan

Characterization of washout is different

- At CEUS, all types of malignant nodules show “washout” - HCC, metastasis, intrahepatic cholangiocarcinoma (ICC), hepato-cholangiocarcinoma. Unlike CT or MRI with extracellular contrast agents (ECA), ICC and other fibrotic tumors do not show sustained enhancement or progressive concentric enhancement
- Implication:
  - Differentiation of HCC from ICC requires careful characterization of “timing” and “degree” of washout. Documenting the “presence” of washout is only suggestive of malignancy, and not helpful to differentiate HCC from non-HCC malignancy
- Explanation:
  - The contrast agents have different kinetics: blood pool vs ECA

Distinction between 10-19 and ≥ 20 mm nodules is not relevant for LI-RADS categorization

- Implication: changes criteria for LR-3, -4, -5
- Justification:

Study	Journal	Year	Inclusion Criteria	Cirrhosis	Final diagnosis, number of the patients	Diagnostic criteria	Specificity	PPV
Pompili, et al [2]	Digestive and Liver Disease	2008	small (10 -30 mm) liver nodules in 55 patients with cirrhosis	all	62 (41 measuring 1.0-2.0 cm, 21 measuring 2.1-3.0 cm)	FNA, imaging	100	100
Forner, et al [3]	Hepatology	2008	small (≤ 20mm)) FLL in patients with cirrhosis	all	89 HCC (n=60), cholangiocarcinoma (n=1), benign lesions (n=28)	FNA	93	94
Jang, et al [4]	Eur J Radiol	2009	small nodules (10-20mm) with high-risk for HCC	all	59 (26/33) (benign/malignancy)	LT, Bx, resection or clinical & imaging f/u	100	100
Leoni, et al [5]	Am J Gastro	2010	small (10 -30 mm) liver nodules in 60 patients with cirrhosis	all	75 (44/31) (benign/malignancy)	superparamagnetic iron oxide MRI	94	94
Sangiovanni, et al [6]	GUT	2010	small (10 -20 mm) liver nodules in patients with cirrhosis	all	21/34 (benign/malignancy)	CT; MRI; FNA	100	100
Leoni, et al [7]	Ultraschall in Med	2013	small (10-30mm)) FLL in patients with cirrhosis	all	127 HCC (71 primary, 56 recurrent) 10-20mm 73 nodules (55 HCC, 18 non HCC)	biopsy	94	94
Manini, et al [8]	J Hepatol	2014	HCC in patients with cirrhosis (7 <1 cm, 67 1-2 cm, 45 >2 cm)	all	119 (84 HCC) 7<1cm, 67 1-2cm, 45>2cm	MRI (1-2cm nodules), CT (>2 cm), FNB	100	100
Shin, et al [9]	Digestive and Liver Disease	2015	small (< 30 mm) atypical HCC in patients with cirrhosis	all	46 (9/37)7 dysplastic nodules (median 1.5cm, 1-2cm), Edmondson grade I HCC (median 1.6cm, 1-2.5cm), Edmondson II HCC (median 1.8cm (1-2.9cm)	biopsy	100	100

Meta-analysis on sensitivity and PPV of US, CT, MRI for HCC detection

10. Hanna RF, Miloushev VZ, Tang A, et al. Comparative 13-year Meta-analysis of the Sensitivity and Positive Predictive Value of Ultrasound, CT, and MRI for Detecting Hepatocellular Carcinoma. Abdominal Radiology. 2016;41:71-90

- pooled per-lesion sensitivity (242 studies, 15,713 patients) and PPV (116 studies, 7492 patients):
  - non-contrast-enhanced US (59.3%, 77.4%)
  - contrast-enhanced CT (73.6%, 85.8%)
  - gadolinium-enhanced MRI (77.5%, 83.6%)
  - gadoxetate-enhanced MRI (85.6%, 94.2%)
  - contrast-enhanced US (84.4%, 89.3%)

Threshold growth is not a major feature

- Implication: changes criteria for LR-3, -4, -5
- Justification:
  - Ultrasound has high spatial resolution and can measure the dimensions of nodules and other observations accurately. However, ultrasound does not capture the same imaging plane on serial exams as reliably as CT or MRI. Therefore tumor growth is not used as a major feature on CEUS.
  - Instead, CEUS LI-RADS uses diameter increase as an ancillary feature that favors HCC. CEUS Examiners should exercise judgment in the application of this feature, which applies only to an unequivocal increase in the diameter of an observation

Criteria for some categories have been modified

- LR-5:
  - 10-19 mm vs ≥ 20 mm distinction not relevant for categorizing APHE nodules
  - capsule and threshold growth are not major features for CEUS
  - no LR-5g or LR-5us
- LR-4:
  - 10-19 mm vs ≥ 20 mm distinction not relevant for categorizing APHE nodules
- LR-2:
  - Isoenhancement in all phases
    - Distinct solid nodule <10mm OR
    - Not a distinct solid nodule, any dimension
  - Observation previously LR-3, and stable dimension for 2 years or more
  - Note: observations that are not definitely benign (LR-1) and do not meet the above LR-2 criteria are categorized LR-3 or higher
- LR-1:
  - Categorize observations/nodules as CEUS LR-1, definitely benign, with caution
  - Examples of observations that can be categorized LR-1 if features are diagnostic: Hemangioma, focal fat deposition, focal fat sparing, cyst

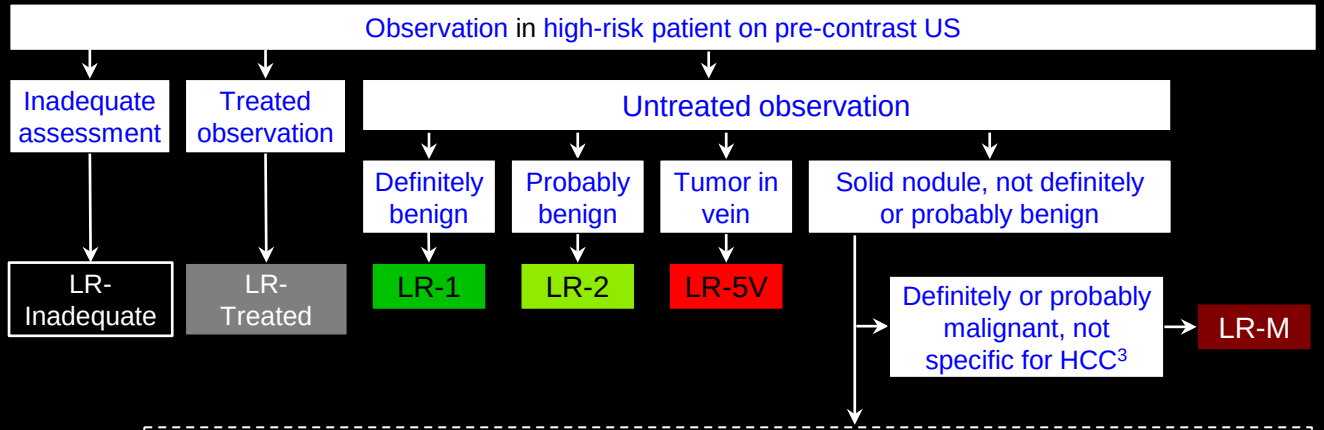
Algorithm for CEUS differs from CT/MRI

- Algorithm was modified from CT or MRI in accordance with the concepts listed on prior slides
- Inserted node to clarify that the Table applies only to solid nodules that are not definitely or probably benign

CEUS LI-RADS

v2016

Algorithm for CEUS



	Arterial phase hypo/isoenhancement		Arterial phase hyperenhancement[1]	
Dimension (mm)	< 20	≥ 20	< 10	≥ 10
No washout of any type	LR-3	LR-3	LR-3	LR-4
Late and mild washout[2]	LR-3	LR-4	LR-4	LR-5

Apply ancillary features and then apply tie-breaking rules to adjust category as appropriate

[1] Arterial phase hyperenhancement: whole or in part, not rim or peripheral discontinuous globular enhancement
[2] Late in onset (≥ 60 seconds) and mild in degree: in whole or in part, with no part showing early or marked washout
[3] Early onset washout (<60seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

LR-1

- Cyst
- Classic hemangioma
- Definite focal hepatic fat deposition or sparing

LR-2

- Isoenhancement in all phases
  - Distinct solid nodule <10mm OR
  - Not a distinct solid nodule, any dimension
- Observation previously LR-3, and stable dimension for 2 years or more

LR-5V

- Definite enhancing soft tissue in vein regardless of visualization of parenchymal mass/nodule

LR-M

Washout Characteristics:
- Early onset washout (< 60sec) and/or marked (punched out) appearance

Arterial phase enhancement
- Rim enhancement

Acknowledgments

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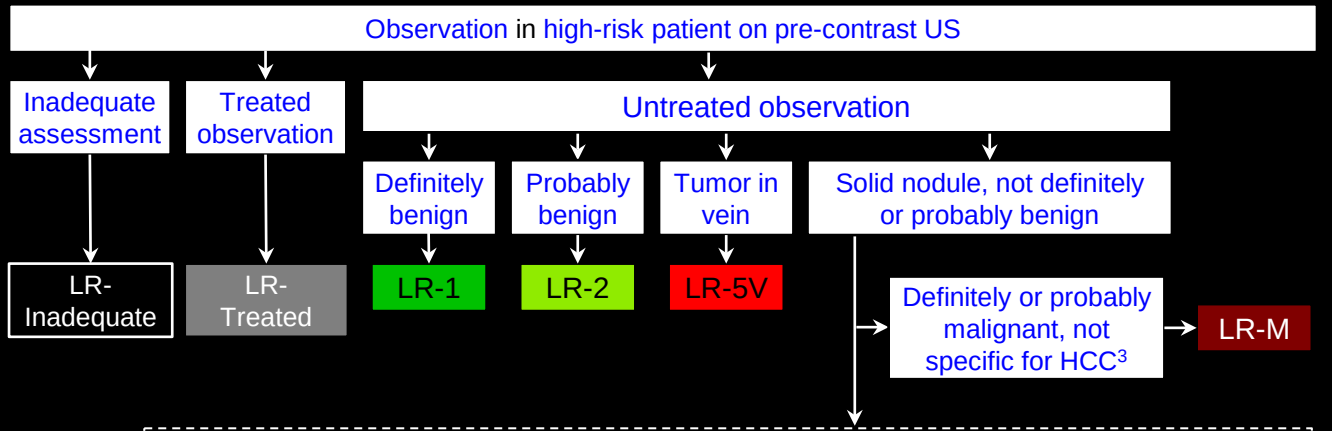
Algorithm for CEUS



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Late and mild washout[2]	LR-3	LR-4	LR-4	LR-5

Apply ancillary features and then apply tie-breaking rules to adjust category as appropriate

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[3] Early onset washout (<60seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

CEUS LR-1: Definitely Benign

Concept:
100% certainty observation is benign

Definition:
- Liver observation with imaging features diagnostic of a definitely benign entity

or
- Definite spontaneous disappearance at follow up

Examples:
- Simple cyst
- Classic hemangioma
- Definite focal hepatic fat deposition
- Definite focal hepatic fat sparing

Management implications
- Continued routine surveillance usually is appropriate

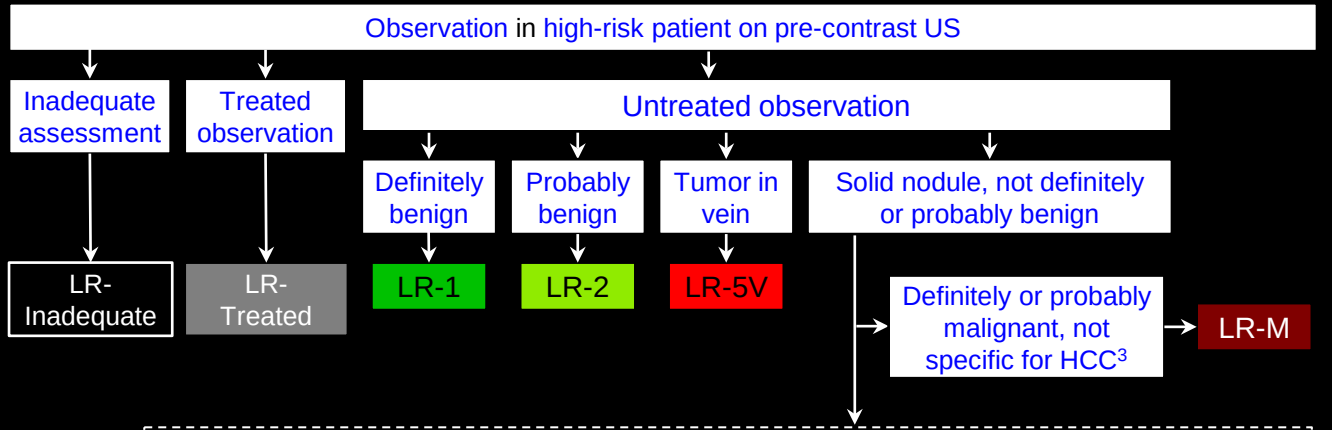
Acknowledgments

CEUS LI-RADS 1

Comments:

- Observations interpreted as definite cysts or hemangiomas at CEUS should be categorized LR-1. If there is uncertainty in the diagnosis, categorize as LR≥2
- Observations interpreted as focal hepatic fat deposition or focal hepatic fat sparing can be categorized LR-1 if and only if the CEUS features are unequivocal and/or if the diagnosis was previously confirmed at CT or MR. If there is uncertainty in the diagnosis, categorize as LR≥2
- Except for simple cyst(s), classic hemangiomas, and some cases of focal hepatic fat deposition or sparing, ultrasound-detectable observations should not be categorized LR-1 in at-risk patients unless the diagnosis of a benign entity was previously established by other tests (CT, MRI, or biopsy)

Algorithm for CEUS



	Arterial phase hypo/isoenhancement		Arterial phase hyperenhancement[1]	
Dimension (mm)	< 20	≥ 20	< 10	≥ 10
No washout of any type	LR-3	LR-3	LR-3	LR-4
Late and mild washout[2]	LR-3	LR-4	LR-4	LR-5

Apply ancillary features and then apply tie-breaking rules to adjust category as appropriate

[1] Arterial phase hyperenhancement: whole or in part, not rim or peripheral discontinuous globular enhancement
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[3] Early onset washout (<60seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

CEUS LR-2: Probably Benign

Concept:
High likelihood observation is benign

Definition:
Liver observation or nodule with imaging features suggestive but not diagnostic of a benign entity

Criteria:
- Isoenhancement in all phases
  - Distinct solid nodule <10mm OR
  - Not a distinct solid nodule, any dimension
- Observation previously LR-3, and stable dimension for 2 years or more

Examples:
- Probable cirrhotic regenerative nodule or low-grade dysplastic nodule

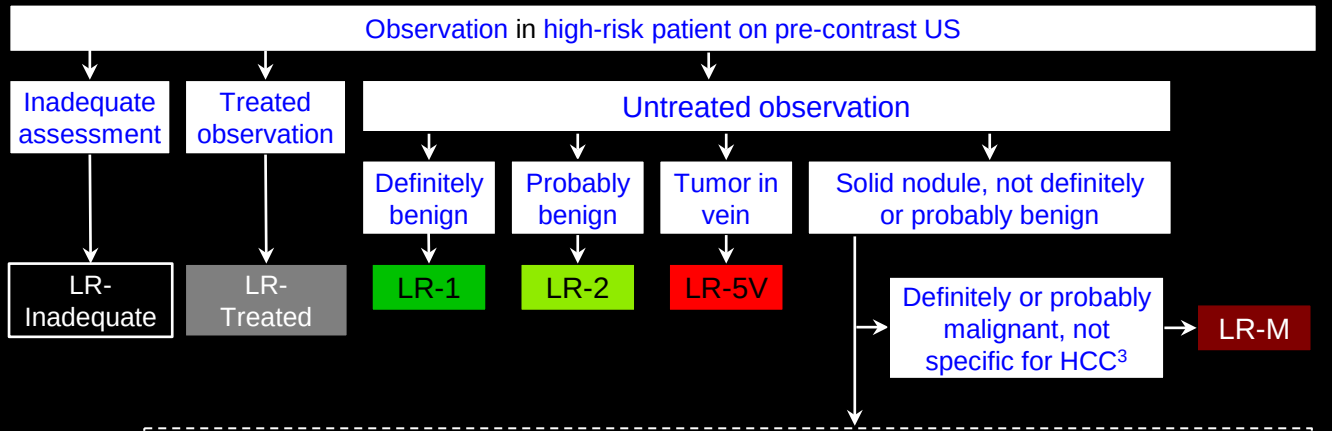
Management implications
- Continued routine surveillance usually is appropriate.

Acknowledgments

CEUS LI-RADS

v2016

Algorithm for CEUS



	Arterial phase hypo/isoenhancement		Arterial phase hyperenhancement[1]	
Dimension (mm)	< 20	≥ 20	< 10	≥ 10
No washout of any type	LR-3	LR-3	LR-3	LR-4
Late and mild washout[2]	LR-3	LR-4	LR-4	LR-5

Apply ancillary features and then apply tie-breaking rules to adjust category as appropriate

[1] Arterial phase hyperenhancement: whole or in part, not rim or peripheral discontinuous globular enhancement
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[3] Early onset washout (<60seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

CEUS LR-3: Intermediate Probability for HCC

Concept:
- Both HCC and benign entity are considered intermediate probability

Definition:
- Distinct solid nodule that does not meet unequivocal criteria for other LI-RADS categories

Criteria:
- ≥ 10mm distinct solid nodule with arterial phase iso-enhancement without washout of any type (isoehnancing in all phases).
- Any size distinct solid nodule with arterial phase hypoenhancement without washout of any type
- < 20mm distinct solid nodule with arterial phase iso or hypoenhancement and mild/late washout
- <10mm distinct solid nodule with APHE (in whole or in part, not rim or peripheral discontinuous globular enhancement) and without washout of any type

Management implications
- Appropriate management is variable, depending mainly on nodule dimension and stability, as well as clinical considerations.
- Please see Management section for details.

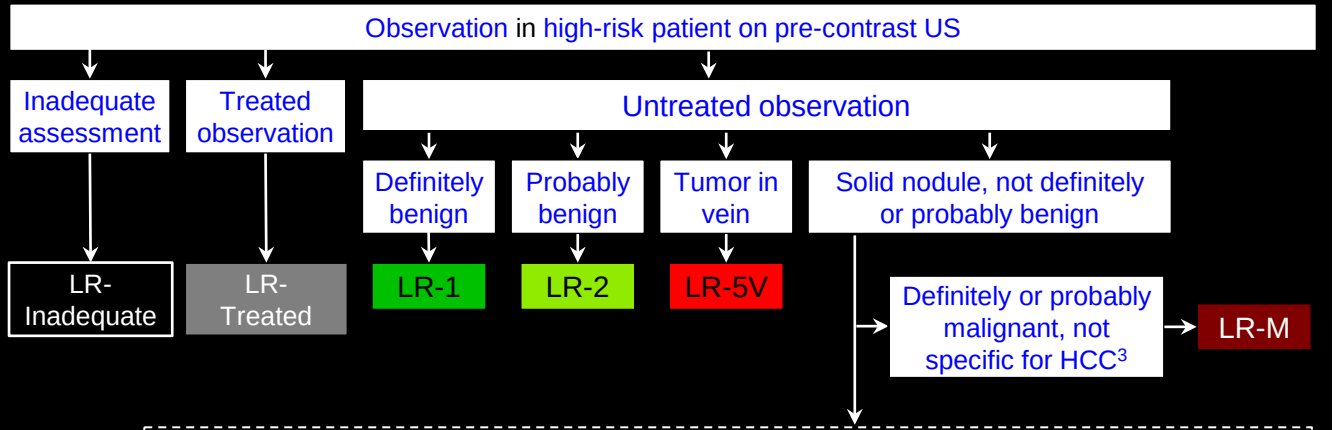
Acknowledgments

Feedback? Email RADS@acr.org

CEUS LI-RADS

v2016

Algorithm for CEUS



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No washout of any type	LR-3	LR-3	LR-3	LR-4
Late and mild washout[2]	LR-3	LR-4	LR-4	LR-5

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[3] Early onset washout (<60seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

CEUS LR-4: Probably HCC

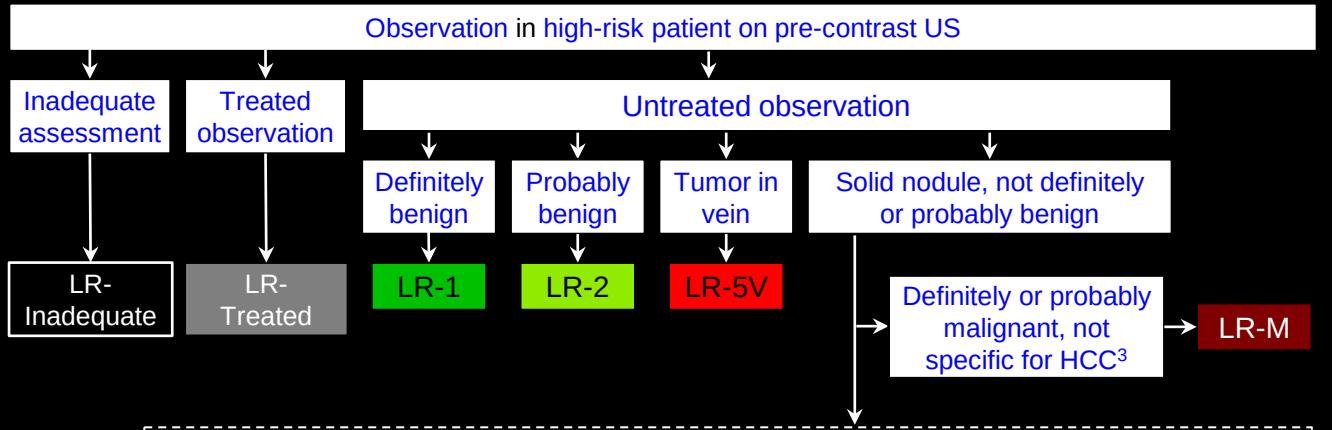
Concept:
Observation is probably HCC but there is not 100% certainty

Definition:
Distinct solid nodule with imaging features suggestive but not diagnostic of HCC

Criteria:
- ≥ 20mm distinct solid nodule with arterial phase hypo or isoenhancement with mild and late washout
- < 10mm distinct solid nodule with APHE (in whole or in part, not rim or globular peripheral enhancement) with mild and late washout
- ≥ 10mm distinct solid nodule with APHE (in whole or in part, not rim or peripheral discontinuous globular enhancement) without washout of any type

Management implications
- Please see Management section for details

Algorithm for CEUS



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No washout of any type	LR-3	LR-3	LR-3	LR-4
Late and mild washout[2]	LR-3	LR-4	LR-4	LR-5

Apply ancillary features and then apply tie-breaking rules to adjust category as appropriate

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[3] Early onset washout (<60seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

CEUS LR-5: Definitely HCC

Concept:
100% certainty observation is HCC.

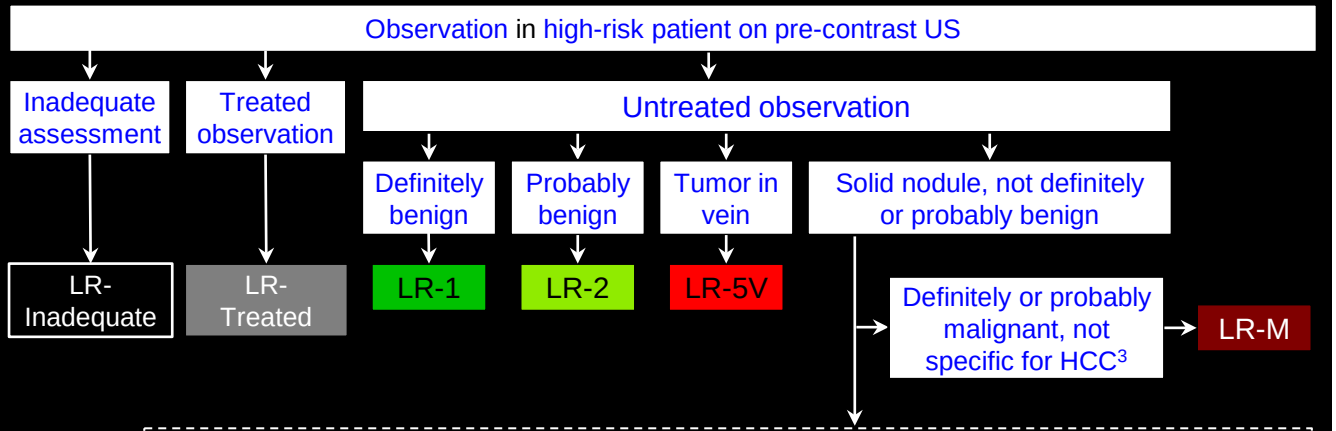
Definition:
Distinct solid nodule with imaging features diagnostic of HCC

Criteria:
- ≥10mm distinct solid nodule with APHE (in whole or in part, not rim or peripheral discontinuous globular enhancement) with mild and late washout

Management
- Proceed with treatment for HCC

Acknowledgments

Algorithm for CEUS



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No washout of any type	LR-3	LR-3	LR-3	LR-4
Late and mild washout[2]	LR-3	LR-4	LR-4	LR-5

Apply ancillary features and then apply tie-breaking rules to adjust category as appropriate

[1] Arterial phase hyperenhancement: whole or in part, not rim or peripheral discontinuous globular enhancement
[2] Late in onset (≥ 60 seconds) and mild in degree: in whole or in part, with no part showing early or marked washout
[3] Early onset washout (<60seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

CEUS LR-5V: Definite tumor in vein

Concept:
100% certainty there is tumor within the vein

Definition:
Observation associated with definite tumor in vein

Synonyms
Tumor thrombus in vein
Macrovascular invasion

RADLEX ID: (RID39483: Tumor in vein)

Criteria:
Definite enhancing soft tissue in vein regardless of visualization of parenchymal mass/nodule
- Must have definite enhancement to some degree in the arterial phase followed by washout (regardless of onset or degree)

Implications:
- Categorizes patient as locally advanced stage

Acknowledgments

CEUS LI-RADS 5V

Comments:

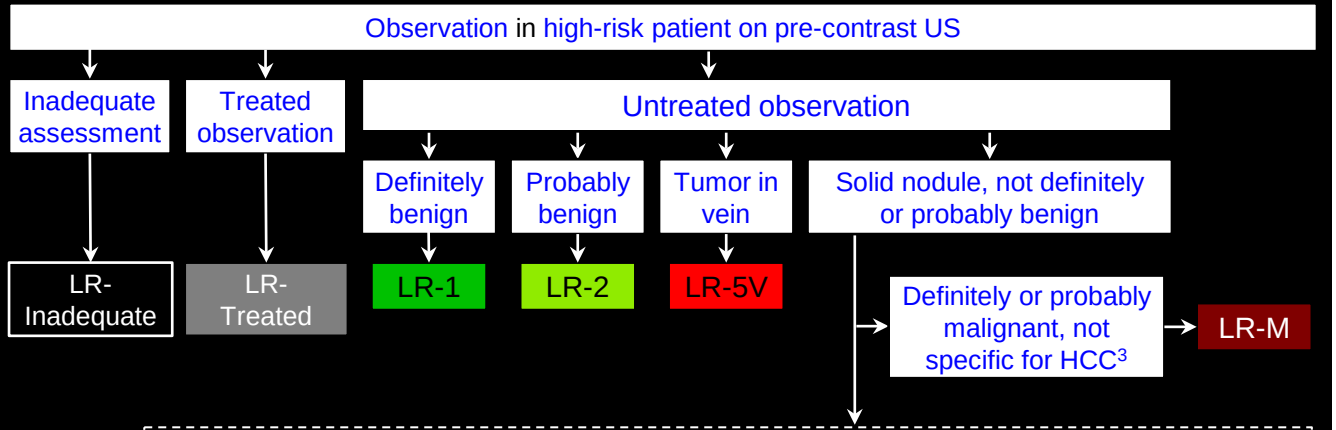
- LR-5V applies even if a parenchymal component of mass is not identified at imaging
- The term tumor in vein is preferred to tumor thrombus

  Rationale: the pathological spectrum ranges from thrombus with scant tumor cells to solid tumor with scant thrombus
- While not diagnostic of tumor in vein, features that may alert examiners to diagnosis include:
  - Occluded or partially occluded vein with any of the following:
    - Moderately to markedly expanded lumen
    - Ill-defined or frankly disrupted walls
    - Contiguity with LR-5 nodule
- By comparison, non-neoplastic bland thrombus does not enhance, usually does not expand the vein lumen to same degree and preserves the vein walls

Potential pitfalls and challenges

- Although differentiation of complete occlusive thrombus from tumor in vein is usually straightforward at CEUS, differentiation of partially occlusive bland thrombus from tumor in vein may be challenging. With complete occlusion, there is no enhancement within the occluded vein in any phase, which permits reliable diagnosis of bland thrombus. With non-occlusive thrombus, however, venous flow around the intraluminal clot or in the recanalized lumen may be mistaken for arterial vascularity and misdiagnosed as tumor within vein. To reliably differentiate tumor in vein vs. partially occlusive/recanalized bland thrombus, careful assessment of the arrival time of contrast to the vein is needed:
  - Early arrival of contrast material into the soft tissue in the vein at about the same time as opacification of hepatic arteries suggests tumor
  - Arrival of contrast material several (~10) seconds after opacification of hepatic arteries favors venous flow around a non-occlusive bland thrombus
  - Confirmation of arterial wave flow on spectral Doppler may be of additional help in differentiating tumor within vein from non-occlusive bland thrombus
- Tumor in peripheral portal veins may be mistaken for tumor nodules, erroneously downstaging the patient. Avoidance is facilitated by real-time imaging while sweeping through the liver, especially in the portal phase, to depict the tubular configuration of the tumor and its continuity with more central portal or hepatic veins

Algorithm for CEUS



	Arterial phase hypo/isoenhancement		Arterial phase hyperenhancement[1]	
Dimension (mm)	< 20	≥ 20	< 10	≥ 10
No washout of any type	LR-3	LR-3	LR-3	LR-4
Late and mild washout[2]	LR-3	LR-4	LR-4	LR-5

Apply ancillary features and then apply tie-breaking rules to adjust category as appropriate

[1] Arterial phase hyperenhancement: whole or in part, not rim or peripheral discontinuous globular enhancement
[2] Late in onset (≥ 60 seconds) and mild in degree: in whole or in part, with no part showing early or marked washout
[3] Early onset washout (<60seconds) and/or marked (punched out) appearance and/or arterial phase rim enhancement

CEUS LR-M: Definitely or Probably Malignant, not specific for HCC

Concept:
Observation is probably or definitely malignant, but imaging features are not specific for HCC

Definition:
Distinct solid nodule with one or more imaging features that favor non-HCC malignancy

Criteria:
- 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 liver within 60 seconds of contrast injection
  - Marked washout resulting in a “punched out” appearance
- Arterial phase rim enhancement, followed by washout (regardless of onset or degree)

Management
- Variable, depending on type of malignancy suspected
- Biopsy is frequently needed for a LR-M categorization as there is a lack of specificity for a diagnosis

Acknowledgments

CEUS LI-RADS M

Comments:

- Distinct solid nodules with enhancement of any degree or morphology in the arterial phase followed by marked early washout should be categorized LR-M
- Distinct solid nodules with mild and late washout may be categorized LR-3, LR-4, LR-5, or LR-5V depending on other features. Such washout is slow in onset (onset after 60 seconds) and mild in degree

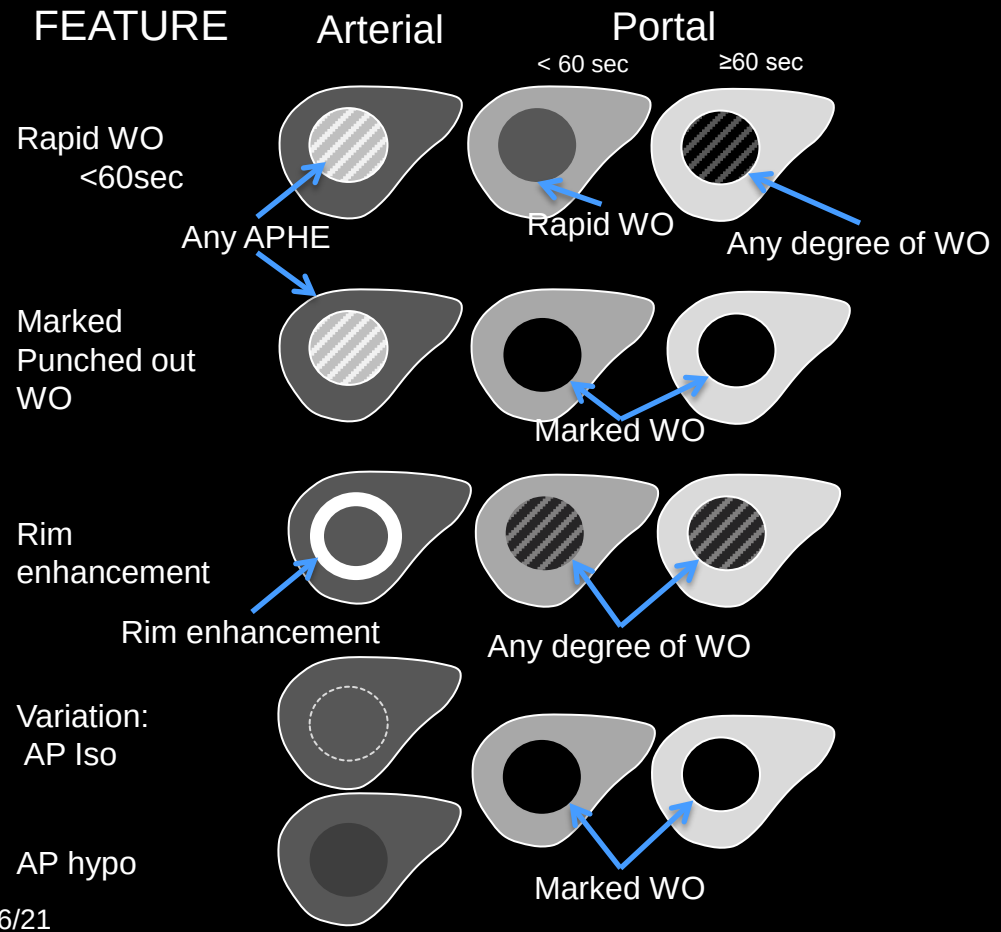
Potential pitfalls and challenges

- Inflammatory masses, especially inflammatory pseudotumors, generally show APHE and early marked washout on CEUS[11)]

Reference:

11. Kong WT, Wang WP, Cai H, Huang BJ, Ding H, Mao F. The analysis of enhancement pattern of hepatic inflammatory pseudotumor on contrast-enhanced ultrasound. Abdom Imaging 2014;39:168-74.

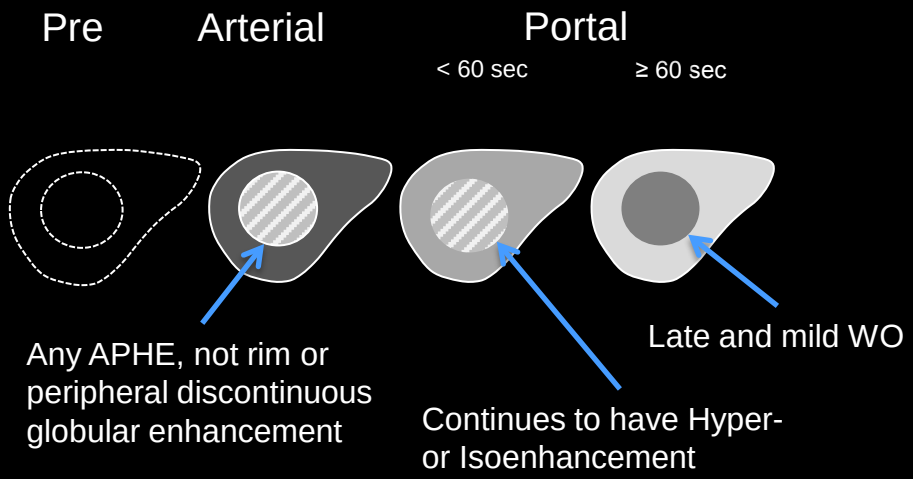
Kinetics of CEUS Washout LR-M



Arterial phase enhancement	Onset of washout (Timing)	Degree of washout
APHE* (in whole or in part, not rim or hemangioma pattern)	<60 sec	Any degree
APHE (in whole or in part, not rim or peripheral discontinuous globular enhancement)	Any	Marked/ punched out
Rim Enhancement	Any	Any
Iso or hypo-enhancement	Any	Marked/ punched out

*APHE: arterial phase hyperenhancement
WO: washout

Kinetics of CEUS Washout LR-5



Arterial phase enhancement	Onset of washout (Timing)	Degree of washout
APHE* (in whole or in part, not rim or peripheral discontinuous globular enhancement)	≥ 60 sec*	Mild washout (not marked or punched out)
Caveat: later marked washout, following initial weak washout suggest HCC and is classified as LR-5		

Long observation up to ~ 5 minutes as long as enhancement lasts is essential to avoid missing late, weak washout

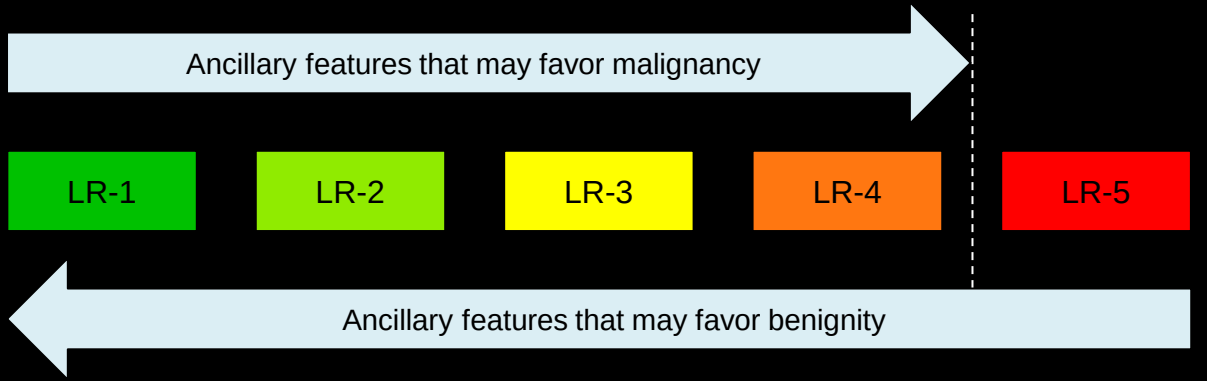
References for Washout Timing*:
12) Han J, Liu Y, Han F, et al. Ultrasound in medicine & biology 2015;41:3088-95.
13) de Sio I, Iadevaia MD, Vitale LM, et al. United European Gastroenterol J 2014;2:279-87.
14) Li R, Yuan MX, Ma KS, et al. PLoS One 2014;9:e98612.

Washout features

Degree	Onset: Early	Onset: Late
Marked	LR-M Characteristic of ICC and metastases. Categorize as LR-M	LR-M Suggestive of malignancy in general, not specific for any particular malignancy Categorize as LR-M *Rationale: avoid false positive diagnosis of HCC*
Mild	LR-M Suggestive of malignancy in general, not specific for any particular malignancy Categorize as LR-M *Rationale: avoid false positive diagnosis of HCC*	LR-3 or LR-4 or LR-5 Characteristic of HCC and precursor nodules in hepatocarcinogenesis spectrum Categorize as LR-3 or LR-4 or LR-5

Ancillary features that may favor malignancy may be applied to upgrade category by one or more categories (up to but not beyond LR-4). They cannot be used to upgrade to LR-5. Absence of these features should not be used to downgrade the LR category.

- Unequivocal diameter increase
- Nodule-in-nodule architecture



Ancillary features that may favor benignity may be applied to downgrade category by one or more categories. Absence of these features should not be used to upgrade the LR category.

- Unequivocal diameter reduction
- Diameter stability ≥ 2 years

Ancillary features

Definition:
Imaging features that modify the likelihood of HCC. In isolation, these features do not permit reliable categorization of observations and hence are considered ancillary.

Comments:
Examiners may at their discretion apply ancillary features to adjust LI-RADS category as follows:

- Features that may favor malignancy to upgrade category by one or more categories (up to but not beyond LR-4).
  - Ancillary features cannot be used to upgrade category to LR-5 Ancillary features that may favor malignancy can favor malignancy in general or specifically favor HCC
- Features that may favor benignity to downgrade category by one or more categories.

Features that may favor malignancy:
- Unequivocal diameter increase
- Nodule-in-nodule architecture*

*Features that specifically favor HCC as opposed to malignancy in general.

Features that may favor benignity:
- Unequivocal dimension reduction
- Dimension stability ≥ 2 years

Appendix

CEUS LI-RADS Training Requirements

Overview:

CEUS LI-RADS Training requirements are adapted from and closely resemble those advocated by EFSUMB. Whereas EFSUMB recommendations address CEUS imaging generally, CEUS LI-RADS focuses on technical aspects specifically relevant to liver imaging in patients at risk for HCC. The CEUS LI-RADS requirements will be refined as experience accrues and in response to user feedback.

CEUS Training Requirements

Levels of Training and Practice

According to the EFSUMB's Minimal US Training Recommendations, the practice of conventional medical US is classified into one of three levels: Level 1, Level 2 and Level 3. The definitions of these levels is provided in the EFSUMB guidelines[2].

Level 2 is recommended before beginning to learn the practice of CEUS. Level 3 is recommended before teaching the practice of CEUS. Levels 2 and 3 are discussed in the next few slides. Level 1 is not further discussed.

Reference:
15. Education, Practical Standards Committee, European Federation of Societies for Ultrasound in Medicine and Biology. Minimum training recommendations for the practice of medical ultrasound. Ultraschall Med 2006;27(1):79-105

LI-RADS v2016

CEUS Training Requirements for Liver Imaging in the High-Risk Patient

Level 2 Knowledge Base and Technical Capabilities

- Basic knowledge about contrast agents (CA) available
- Extensive experience with and knowledge in using ultrasound equipment for contrast imaging
- To be familiar with the indications and contraindications for the use of CA
- To be able to recognize and minimize artifacts linked to the use of CA
- To be prepared to recognize and manage rare anaphyllactoid reactions caused by the CA
- To understand the effect of ultrasound exposure on CA, including the time- and ultrasound power-dependent degradation of the CA following injection
- To be able to assess the technical quality and adequacy of the exam
- To be able to recognize and correctly diagnose common liver pathologies
- To be aware of one's own knowledge and technical limitations and to be able to recognize when referral to a more experienced practitioner or to a more technically advanced center is appropriate

Reference:
Modified from 16. Education, Practical Standards Committee, European Federation of Societies for Ultrasound in Medicine and Biology. Minimum training recommendations for the practice of medical ultrasound. Appendix 14: (CEUS) CONTRAST ENHANCED ULTRASOUND
" issuu.com/efsumb/docs/appendix14ceus/2

CEUS Training Requirements for Liver Imaging in the High-Risk Patient

After Proper education for level 2, the trainee is able to:

- Perform a thorough CEUS examination of the liver in adults without and with cirrhosis, and spanning a wide spectrum of body habitus from thin to obese according to the present EFSUMB Minimum Requirements including documentation of appropriate cine loop storage during all relevant contrast phases
- Recognize focal liver nodules and other lesions as well as vascular abnormalities
- Recognize the CEUS appearance after locoregional treatment
- Generate an appropriate report according to CEUS LI-RADS requirements
- Correlate imaging features of abnormalities depicted at CEUS with those depicted at other modalities (e.g., CT, MRI)

Reference:
Modified from 16. Education, Practical Standards Committee, European Federation of Societies for Ultrasound in Medicine and Biology. Minimum training recommendations for the practice of medical ultrasound. Appendix 14: (CEUS) CONTRAST ENHANCED ULTRASOUND
“ issuu.com/efsumb/docs/appendix14ceus/2

CEUS Training Requirements for Liver Imaging in the High-Risk Patient

Level 3 examiner who can teach and perform research in CEUS should be able:

- To give off-line second opinions on exams by level 2 CEUS examiners
- To perform technically difficult CEUS exams referred by level 2 examiners
- To perform specialized CEUS examinations
- To perform advanced CEUS-guided invasive procedures
- To conduct substantial research in CEUS
- To teach CEUS at all levels
- To be aware of and to pursue developments in CEUS

Reference:
Modified from 16. Education, Practical Standards Committee, European Federation of Societies for Ultrasound in Medicine and Biology. Minimum training recommendations for the practice of medical ultrasound. Appendix 14: (CEUS) CONTRAST ENHANCED ULTRASOUND " issuu.com/efsumb/docs/appendix14ceus/2

LI-RADS v2016

CEUS Training Requirements for Liver Imaging in the High-Risk Patient

General Recommendations for Training and Qualification

- Trainees should attend an appropriate theoretical course before starting practical work
- Practical CEUS training at level 2 should be supervised by a CEUS experienced level 3 examiner. The required duration of training has not yet been standardized
- During the practical phase, trainees should develop experience performing CEUS examinations encompassing the full range of pathological conditions of the liver in adults. This includes adults without and with cirrhosis of varying severity and spanning a wide range of body habitus from thin to morbidly obese
- The following documentation should be maintained:
  - A log book listing the types of liver examinations and their indications
  - Competency assessment sheet
  - Documented cine loops with diagnosis and imaging report should be sent to a level 3 site or level 3 practitioner at the same institution for re-evaluation

Reference:
Modified from 16. Education, Practical Standards Committee, European Federation of Societies for Ultrasound in Medicine and Biology. Minimum training recommendations for the practice of medical ultrasound. Appendix 14: (CEUS) CONTRAST ENHANCED ULTRASOUND
“ issuu.com/efsumb/docs/appendix14ceus/2

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13. de Sio I, Iadevaia MD, Vitale LM, et al. Optimized contrast-enhanced ultrasonography for characterization of focal liver lesions in cirrhosis: A single-center retrospective study. United European Gastroenterol J 2014;2:279-87.
14. Li R, Yuan MX, Ma KS, et al. Detailed analysis of temporal features on contrast enhanced ultrasound may help differentiate intrahepatic cholangiocarcinoma from hepatocellular carcinoma in cirrhosis. PLoS One 2014;9:e98612.
15. Education, Practical Standards Committee EFSUMB, Biology. Minimum training recommendations for the practice of medical ultrasound. Ultraschall Med 2006;27:79-105.
16. Education, Practical Standards Committee EFSUMB, Biology. Minimum training recommendations for the practice of medical ultrasound Appendix 14: (CEUS) CONTRAST ENHANCED ULTRASOUND “ issuu.com/efsumb/docs/appendix14ceus/2