Course: Clinical Cancer MRI: Case-Based
Session: Guidelines & Reporting Standards
Lecture: Liver MRI and HCC (LI-RADS)
Date: Sunday May 31, 2015
Speaker: Claude B. Sirlin, MD
Speaker email: csirlin@ucsd.edu
Speaker institution: Liver Imaging Group, Dept. of Radiology, UC–San Diego, USA

Highlights:

- Hepatocellular carcinoma (HCC) is the second leading cause of cancer death in the world and most rapidly growing cause of cancer death in the United States
- Magnetic resonance imaging (MRI) plays a critical role in the management of patients with or at risk for HCC.
    - In such patients, MRI can be used to make the non-invasive diagnosis of HCC without confirmatory biopsy.
    - Major treatment decisions such as resection, liver transplantation, use of embolic or ablative therapy, and administration of chemotherapy may be made without tissue sampling.
- The Liver Imaging Reporting And Data System (LI-RADS) is a system of standardized terminology, interpretation, and reporting for imaging examinations of the liver [1].
    - It has been developed with the support of the American College of Radiology
    - It is the only radiologic system for HCC developed by a radiology organization
    - It applies to patients with patients at risk for HCC (cirrhosis, chronic hepatitis B viral infection)
    - It addresses both extracellular and hepatobiliary contrast agents
- LI-RADS categorizes observations from LR-1 to LR-5, reflecting probability of benignity or HCC in at-risk patients. Smaller obeservations must satisfy stricter criteria to be assigned an equivalent LR category.
- Observations with features suggestive of non-HCC malignancy are categorized LR-M.
- Observations associated with tumor in vein are categorized LR-5V.
- LR-5 applies to observations with imaging features diagnostic of HCC (or path-proven HCC).
    - The imaging criteria have high specificity but modest sensitivity for HCC.
    - Imaging features relevant for LR-5 categorization are diameter, arterial phase hyper-enhancement, washout appearance, capsule appearance, and threshold growth.
    - These are features of progressed HCC (which characteristically is “hypervascular”), not of early HCC (which characteristically is “hypovascular”).
- Extracellular agents and hepatobiliary agents may be used in LI-RADS categorization.
- Both types of agents have advantages and disadvantages for LI-RADS categorization.
    - Some imaging features unique to or demonstrated to greatest advantage with gadoxetic acid (e.g., transitional phase hypo-intensity and hepatobiliary phase hypointensity) are ancillary features that may favor malignancy. Due to these features, MRI performed with gadoxetic acid provides higher per-lesion sensitivity for high-grade dysplastic nodules and early HCCs. Most such nodules are categorized LR-3 or LR-4.

- Based on theoretical considerations, however, some major features (arterial phase hyper-enhancement, washout appearance, capsule appearance) may be more difficult to characterize with gadoxetic acid than other MR contrast agents, which may make LR-5 categorization more difficult, but this has not been proven in prospectively designed studies.

Target audience:

Physicians, Imaging scientists/engineers, technologists and other health professionals with a developing need for utilizing MRI applications in cancer and personalized care.

Objectives:

As a result of the information presented in this talk, learners will be able to:

- Understand the need for standardized interpretation and reporting of MR imaging examinations done for diagnosis or staging of HCC in patients with cirrhosis or other risk factors for HCC
- Become familiar with and understand key LI-RADS terminology and concepts
- Become familiar with some pitfalls in interpretation
- Apply LI-RADS v2014 algorithm to categorize observations in patients with or at risk for HCC

LI-RADS 2014 Categories

CATEGORIES		
LR-1	Definitely Benign	**Concept:** 100% certainty observation is benign. **Definition:** Observation with imaging features diagnostic of a benign entity, or definite disappearance at follow up in absence of treatment.
LR-2	Probably Benign	**Concept:** High probability observation is benign. **Definition:** Observation with imaging features suggestive but not diagnostic of a benign entity.
LR-3	Intermediate probability for HCC	**Concept:** Both HCC and benign entity have moderate probability. **Definition:** Observation that does not meet criteria for other LI-RADS categories.
LR-4	Probably HCC	**Concept:** High probability observation is HCC but there is not 100% certainty. **Definition:** Observation with imaging features suggestive but not diagnostic of HCC.
LR-5	Definitely HCC	**Concept:** 100% certainty observation is HCC. **Definition:** Observation with imaging features diagnostic of HCC or proven to be HCC at histology.
LR-5V	Definitely HCC with Tumor in Vein	**Concept:** 100% certainty that observation is HCC invading vein. **Definition:** Observation with imaging features diagnostic of HCC invading vein.
LR-M	Probably Malignant, not specific for HCC	**Concept:** Observation is probably malignant, but imaging features are not specific for HCC. **Definition:** Observation with imaging features suggestive of non-HCC malignancy.
LR-Treated	Treated Observation	**Concept:** A loco-regionally treated observation. **Definition:** Observation of any category that has undergone loco-regional treatment.

LI-RADS 2014 Major Features

Untreated observations that are neither definitely nor probably benign and lack features of non-HCC malignancy or tumor in vein may be categorized LR-3, LR-4, or LR-5. Appropriate categorization of such observations depends on the presence of major features. Major features are those that have been shown in prior studies to permit reliable diagnosis of HCC or that have been endorsed by other leading organizations

such AASLD or OPTN. Major features include: arterial phase hypo- or iso-enhancement, arterial phase hyper-enhancement, diameter, washout appearance ("washout"), capsule appearance ("capsule"), and threshold growth. Each of these major features is defined in Table below.

<table>
<tr><th>Major Feature</th><th>Definition</th></tr>
<tr><td>Arterial phase hyper-enhancement</td><td>Enhancement in the arterial phase that unequivocally is greater than that of liver.</td></tr>
<tr><td>Arterial phase hypo- or iso-enhancement</td><td>Enhancement in the arterial phase that is less than that or equivalent to that of liver.</td></tr>
<tr><td>Diameter</td><td>The largest dimension (outer edge to outer edge) of an observation.</td></tr>
<tr><td>Washout appearance ("washout")</td><td>Visually assessed temporal reduction in enhancement relative to liver from an earlier to a later phase resulting in portal venous phase hypo-enhancement or delayed phase hypo-enhancement.</td></tr>
<tr><td>Capsule appearance ("capsule")</td><td>Peripheral rim of smooth hyper-enhancement in the portal venous phase or delayed phase that unequivocally is thicker or more conspicuous than the rims surrounding background nodules.</td></tr>
<tr><td>Threshold Growth</td><td>Diameter increase of a mass by a minimum of 5mm and, depending on the time interval between examinations, by the following amounts:
<table>
<tr><th>Time interval</th><th>Diameter increase</th></tr>
<tr><td>≤ 6 months</td><td>≥ 50%</td></tr>
<tr><td>> 6 months</td><td>≥ 100%</td></tr>
</table>
A new ≥10mm mass also represents threshold growth, regardless of the time interval. A new <10mm mass does not represent threshold growth.</td></tr>
</table>

A few key concepts and caveats are emphasized here. The text below is nearly verbatim from ref [2].

Arterial phase hyper-enhancement

LI-RADS requires that observations unequivocally enhance more than background liver AND be hyper-intense in the arterial phase to meet criteria for arterial phase hyper-enhancement. This is in contrast to some existing literature that expands the definition of arterial phase hyper-enhancement to include observations that temporally enhance from the pre-contrast phase to the arterial phase, even if they are not hyper-intense to liver in the arterial phase. Observations that enhance from hypo-intense pre-contrast to iso-intense in the arterial phase do not meet current LI-RADS criteria for arterial phase hyper-enhancement.

Peripheral or rim-like arterial phase hyper-enhancement is a feature favoring ICC over HCC. Observations that exhibit rim-like arterial phase hyper-enhancement usually should be categorized LR-M rather than LR-3, LR-4, or LR-5. In general, for an observation to be categorized LR-5, the arterial-phase hyper-enhancement should not be rim-like.

Washout appearance

Washout appearance should be strictly defined by temporal reduction in enhancement from an earlier to a later phase, not by simple comparison of the signal intensities between the nodule and surrounding liver in a single post-arterial phase such as the portal venous or delayed phase. The phases appropriate for assessing washout appearance depend on the gadolinium based contrast agent (GBCA) used.

For gadoxetic acid, washout appearance should be assessed by comparing the portal venous phase to the arterial phase. After the portal venous phase, the hepatic parenchyma continues to progressively enhance due to uptake of gadoxetic acid by hepatocytes. Thus, relative hypo-intensity of an observation after the portal venous phase (e.g., in the transitional phase) may be due to rapid transit of contrast, lack of functional hepatocytes, or a combination of the two. Given this uncertainty, transitional phase hypo-intensity does not have the same diagnostic implication as washout appearance and so should not be used to categorize an observation LR-5. Similarly, the hepatobiliary phase should not be used to gauge washout appearance.

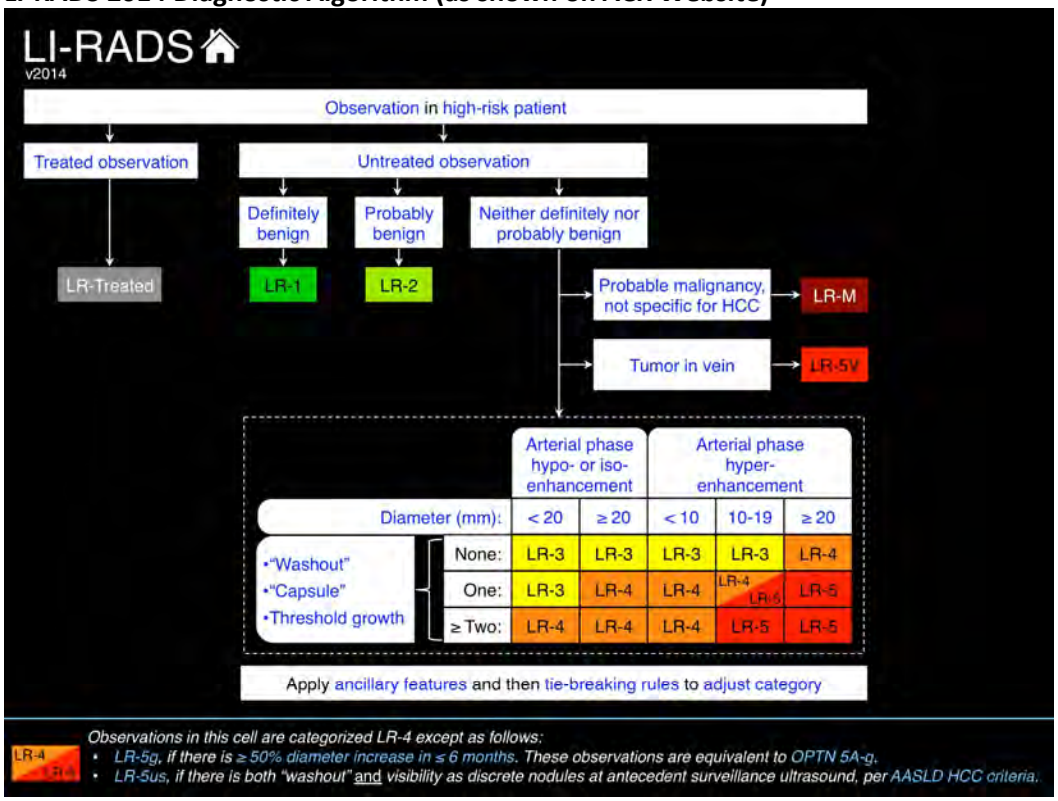
For gadobenate dimeglumine, washout appearance can be assessed by comparing either the portal venous phase or the delayed phase to the arterial phase. Although gadobenate dimeglumine has mild hepatocellular uptake that permits hepatobiliary imaging at a delay of about 1-3 hours, this uptake has negligible impact on enhancement of liver and liver observations during the dynamic phases after its administration. Thus, these phases can be interpreted in the same fashion as with extracellular agents. As with gadoxetic acid, the hepatobiliary phase should not be used to gauge washout appearance.

For extracellular GBCAs, washout appearance can be assessed by comparing either the portal venous phase or the delayed phase to the arterial phase, as these agents have negligible hepatocelluar uptake.

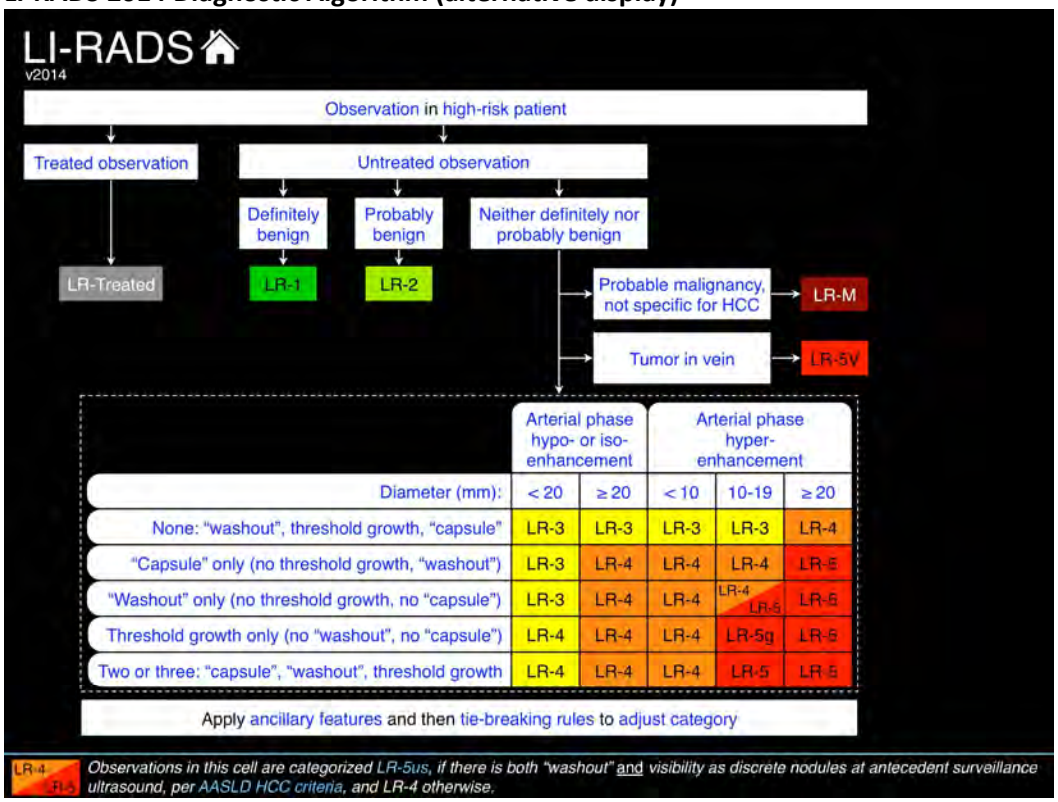
Capsule Appearance

Capsule appearance may be difficult to assess when gadoxetic acid is used. Uptake of gadoxetic acid by hepatocytes leads to progressive enhancement of background liver parenchyma in the transitional phase, which is speculated to obscure any delayed rim enhancement.

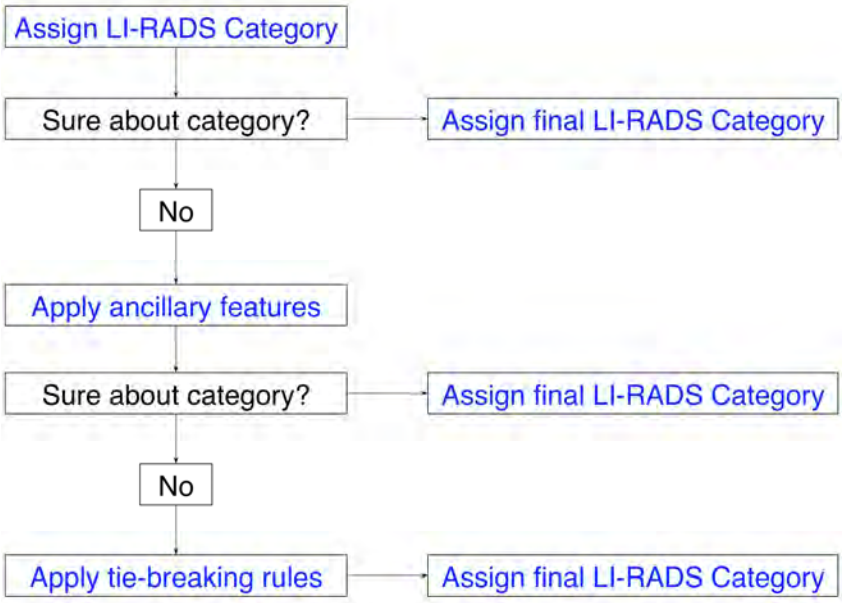
LI-RADS 2014 Diagnostic Algorithm (as shown on ACR Website)



LI-RADS 2014 Diagnostic Algorithm (alternative display)



LI-RADS 2014 Adjustment of Categories

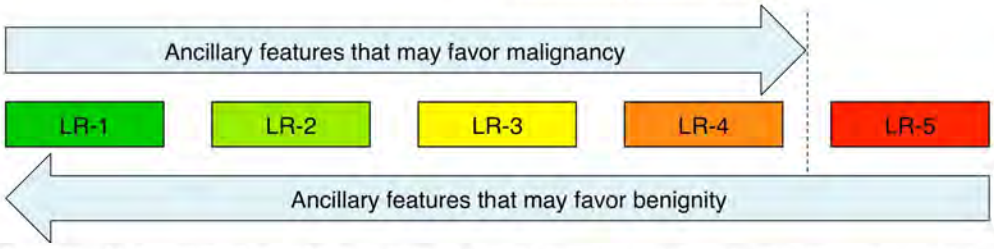


LI-RADS 2014 Ancillary Features

Once an observation has been categorized, radiologists at their discretion may apply ancillary features to adjust the category. Ancillary features are imaging features that modify likelihood of HCC. In isolation, these features do not permit reliable categorization of observations and hence are considered ancillary.

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 category to LR-5. Absence of these features should not be used to downgrade the LR category.

- Mild-moderate T2 hyper-intensity
- Restricted diffusion
- Corona enhancement
- Mosaic architecture
- Blood products
- Diameter increase less than threshold growth
- Nodule-in-nodule architecture
- Intra-lesional fat
- Lesional iron sparing
- Lesional fat sparing
- Distinctive rim
- Hepatobiliary phase hypo-intense rim
- Hepatobiliary phase hypo-intensity

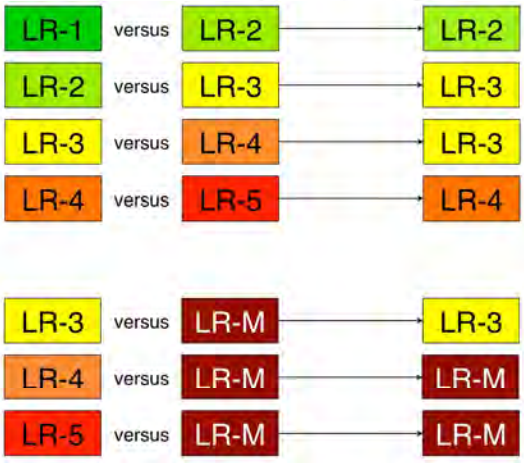


Ancillary features that may favor benignity may be applied to downgrade category by one or more categories. Absence of these features should not be used to upgrade the LR category.

- Undistorted vessels
- Parallels blood pool enhancement
- Diameter reduction
- Diameter stability ≥ 2 years
- Hepatobiliary phase iso-intensity

LI-RADS 2014 Tie-Breaking Rules

Tie-breaking rules: If, after application of ancillary features, a radiologist is still unsure about the final category for an observation, tie-breaking rules should be applied. The tie-breaking rules move observations to a category with a lower degree of certainty.



LI-RADS 2014 Definite and Probable Benign Entities

Definite benign entities	Probable benign entities
Definite • Cyst • Hemangioma • Vascular anomaly • Perfusion alteration • Hepatic fat deposition or sparing • Hypertrophic pseudomass • Confluent fibrosis • Focal scar Observation that spontaneously disappears at follow-up	Probable • Cyst • Hemangioma • Vascular anomaly • Perfusion alteration • Hepatic fat deposition or sparing • Hypertrophic pseudomass • Confluent fibrosis • Focal scar LR-2 cirrhosis-associated nodule

LI-RADS 2014 List of Imaging Features to help differentiate HCC from ICC

Favor HCC	Favor ICC
• Diffuse arterial phase hyper-enhancement • Diffuse washout appearance • Capsule appearance • Distinctive rim • Intralesional fat • Nodule-in-nodule or mosaic architecture • Diffuse T1 hyper-intensity* • Hepatobiliary phase T1 hyper-intensity not attributable to extracellular pooling* • Round or oval shape	• Arterial phase peripheral rim enhancement • Peripheral washout appearance • Portal venous and delayed/transitional phase progressive concentric enhancement • ± Markedly restricted diffusion • Target appearance at DWI • Target appearance in the hepatobiliary phase • Liver surface retraction • Biliary obstruction disproportionate to that expected based on size of mass • Lobulated shape

*Although diffuse T1 hyper-intensity and hepatobiliary phase T1 hyper-intensity are not typical features of HCC, they do not occur in ICC; thus their presence favors a diagnosis of HCC over ICC.

LI-RADS 2014 Features of tumor in vein

Diagnostic of tumor in vein: enhancing soft tissue in lumen of vein

Suggestive but not diagnostic of tumor in vein:

- Occluded vein with any of the following:
  - Moderately to markedly expanded lumen
  - Ill-defined walls
  - Restricted diffusion
  - Contiguity with LR-5 observation
- Obscured, partially visualized vein
- Heterogeneous enhancement of vein not attributable to mixing artifact

References

1. American College of Radiology. Liver Imaging Reporting and Data System version 2014. Accessed February 2015, from http://www.acr.org/Quality-Safety/Resources/LIRADS.
2. Shah A, Santillan C, Tang A, Sirlin CB. Cirrhotic liver: What's that Nodule? -- the LI-RADS approach. JMRI. In press.
3. Santillan CS, Tang A, Cruite I, Shah A, Sirlin CB. Understanding LI-RADS: a primer for practical use. Magn Reson Imaging Clin N Am. 2014 Aug;22(3):337-52. doi: 10.1016/j.mric.2014.04.007. PMID: 25086933
4. Mitchell DG, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): Summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. Hepatology. 2014 Jul 12. doi: 10.1002/hep.27304. [Epub ahead of print] PMID: 25041904
5. Cruite I, Tang A, Sirlin CB. Imaging-based diagnostic systems for hepatocellular carcinoma. AJR Am J Roentgenol. 2013 Jul;201(1):41-55. doi: 10.2214/AJR.13.10570. Review. PMID: 23789657
6. Tang A, Cruite I, Sirlin CB. Toward a standardized system for hepatocellular carcinoma diagnosis using computed tomography and MRI. Expert Rev Gastroenterol Hepatol. 2013 Mar;7(3):269-79. doi: 10.1586/egh.13.3. Review. PMID: 23445236