

# Hepatocellular Carcinoma (HCC): Using Imaging and LI-RADS to Choose Optimal Therapy

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# Hepatocellular Carcinoma

- HCC comprises 90% of the primary liver malignancies worldwide<sup>1</sup>, and is the **second leading cause of cancer death in the world**<sup>2</sup>.
- The most important risk factor is liver cirrhosis; **up to 20% of cases occur in non-cirrhotic patients**<sup>1</sup>.
- The annual incidence is 2-8% in cirrhotic livers and < 0.5% in non-cirrhotic livers<sup>2</sup>.
- Surveillance for HCC is beneficial in patients with certain risk factors<sup>3</sup>.
- Its natural history falls within a continuum shown below<sup>4</sup>.





## In how many of the following patient groups is HCC surveillance recommended<sup>3</sup>? (click for answer)

- Hepatitis C (HCV) cirrhosis
- Hepatitis B (HBV) cirrhosis
- Genetic hemochromatosis and cirrhosis
- Stage 4 primary biliary cirrhosis
- $\alpha$  1-antitrypsin deficiency and cirrhosis

All of these groups would benefit from surveillance!

In addition, the following HBV carriers without cirrhosis would also benefit:

- Asian males >40 years
- Asian females > 50 years
- Africans >20 years
- Family history of HCC

Note: the benefits of surveillance are uncertain in

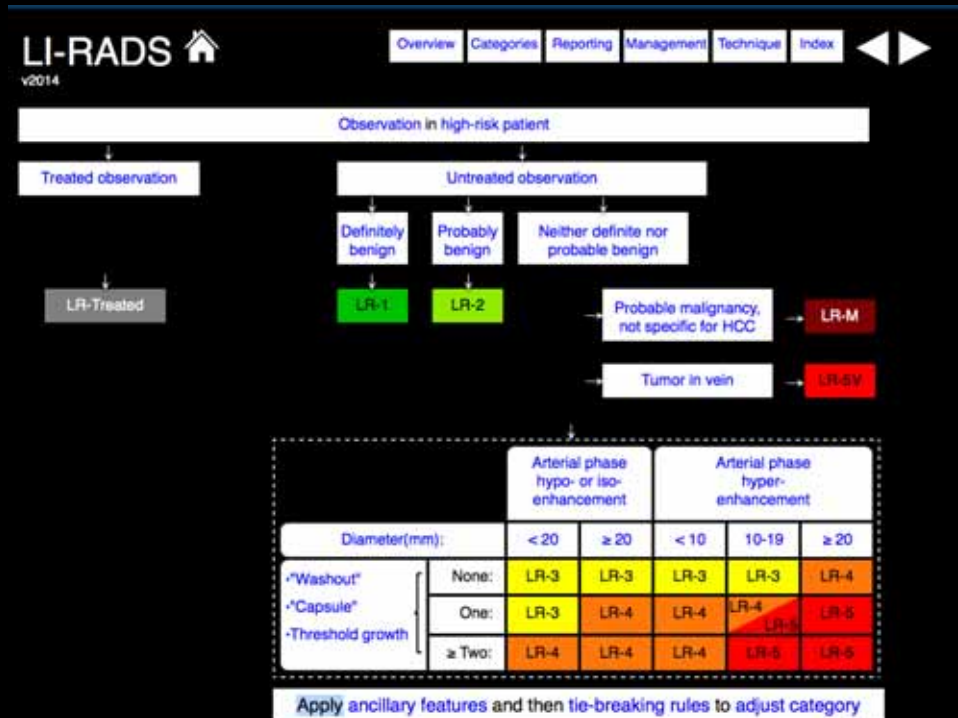
- HBV carriers younger than 40 (males) or 50 years of age (females)
  - Hepatitis C and stage 3 fibrosis
  - Non-cirrhotic NAFLD

# Key Facts in Imaging Assessment of HCC

- Value of imaging in HCC is paramount, as **it can make the diagnosis without a biopsy<sup>5</sup>**.
- Appearance of HCC varies depending on tumor histology.
- Dynamic contrast imaging shows **shift to arterial supply** in the tumor as well as cellular dysplasia<sup>6</sup>.
- Ancillary imaging features support a diagnosis of HCC; more features increase confidence in the diagnosis<sup>6</sup>.
  - **This is the basis of the LI-RADS classification** which is designed to assess hepatic lesions in patients at risk of HCC.

# LI-RADS

- Liver Imaging-Reporting and Data System (LI-RADS) provides a standardized lexicon and algorithm of HCC diagnosis using CT and MR imaging.



**LR-4** Observations in this cell are categorized LR-4 except as follows:

- LR-5g, if there is ≥ 50% diameter increase in ≤ 6 months. These observations are equivalent to QIPN 5A-g.
- LR-5us, if there is both "washout" and visibility as discrete nodules at antecedent surveillance ultrasound, per AASLD HCC criteria.

Summary of the LI-RADS algorithm adapted from <http://nrdcr.ac.org/lirads/>

# LI-RADS Examples

LI-RADS Category	A	B	C	D	
LR-1					<p><b>Typical hemangioma</b> A.T2WI. B,C,D LAVA multiphase. MRI</p>
LR-2					<p><b>Atypical cyst (hydatid cyst)</b> A. simple, B. arterial, C. portal, D. venous. CT</p>
LR-3					<p><b>Intermediate probability of being HCC</b> Mass &lt; 20 mm with arterial hyperenhancement, no wash out, no capsule, stable for 2 years. A. simple, B. arterial, C. venous, D. venous 2 years after. MRI</p>
LR-4					<p><b>Probably HCC</b> Mass &gt; 20 mm with arterial phase hyperenhancement and no additional major features. A. simple, B. arterial, C. portal, D. venous. CT.</p>
LR-5					<p><b>Definitely HCC</b> 40 mm mass with arterial phase hyperenhancement (B,C) with capsule and wash out(D). MRI.</p>

Typical LI-RADS examples; adapted from ECR 2014-C1928

## Using multi-detector CT (MDCT), what is the specificity of arterial hyperenhancement and venous phase washout in cirrhotic livers for HCC?

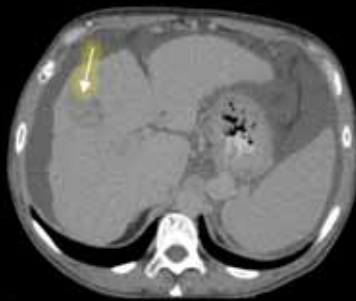
- 60-70%
- 70-80%
- 80-90%
- >90%

These two features, when occurring together, are very specific for HCC<sup>7</sup>. They form its typical enhancement pattern.

The third typical feature is capsule appearance, which is seen in more advanced HCC's.



# Typical Enhancement: Example



Unenhanced



Arterial phase enhancement



Portal venous washout

The typical HCC appearance is seen here in a patient with HCV and alcoholic cirrhosis.

This patient also had a thrombus in the portal vein, which was best seen on the coronal image.





# Ancillary Features Suggestive of Malignancy

HCC tumors do not always show the typical appearance. In those circumstances, ancillary features are used to support the diagnosis. Note that **LR5 cannot be achieved with ancillary features.**

## Features specific for HCC:

- Distinctive rim (different from late capsule)
- Corona enhancement
- Mosaic architecture
- Nodule-in-nodule architecture
- Intra-lesional fat

## Features suggesting malignancy

- Hepatobiliary phase hypo-intensity
- Mild-moderate T2 hyper-intensity
- Restricted diffusion
- Lesional iron or fat sparing
- Blood products
- Diameter increase less than threshold growth

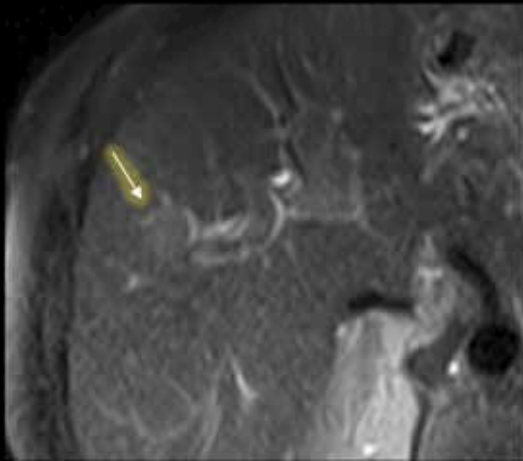
# Imaging Characteristics

As the number of features suggestive of HCC increases, the diagnosis can be made with certainty. Below are the sensitivity and specificity numbers for typical features on MR<sup>2</sup>.

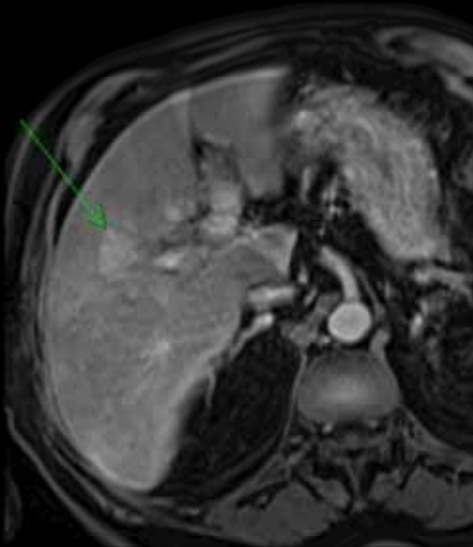
[highlight: most sensitive/specific]

	Sensitivity	Specificity
Arterial hyperenhancement (lesion >20 mm)	82-93%	64-67%
Arterial hyperenhancement (lesion <20 mm)	31-69%	64-67%
Venous phase washout (lesion >20 mm)	53%	80-100%
Venous phase washout (lesion <20 mm)	53%	62-100%
Arterial hyperenhancement with washout	-	96%
Diffusion restriction (lesion <20 mm)	57-94%	87%-88%
Capsule enhancement	43-55%	83-96%
T1W <i>hypointensity</i>	21-91%	70-100%
T2W moderate <b>hyperintensity</b>	21-75%	73-100%
Fat content (micro- or macroscopic)	12-37%	68-100%

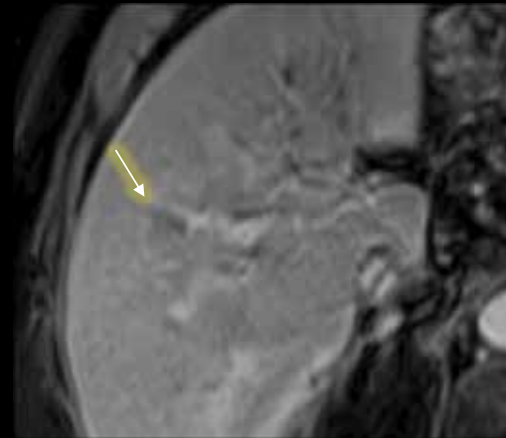
# Typical Appearance on MR Imaging



T2W hyperintense



arterial enhancement



venous washout with capsule

# Atypical Enhancement Pattern

- Up to 40% of HCC's lack obvious arterial phase hyperenhancement<sup>6,8,9</sup>. These cannot be characterized as definite HCC's (LI-RADS 5) and consist mostly of:
  - Early/well-differentiated HCC without development of unpaired arteries<sup>10</sup>.
  - Poorly differentiated infiltrative HCC's<sup>11</sup>.
  - Small HCC's < 2cm<sup>12</sup>.
  - Large HCC > 5 cm with decreased arterial flow due to build-up of intra-tumor pressure<sup>4</sup>.
- Portal venous thrombosis (PVT) increases the likelihood of atypical appearance<sup>15</sup>.

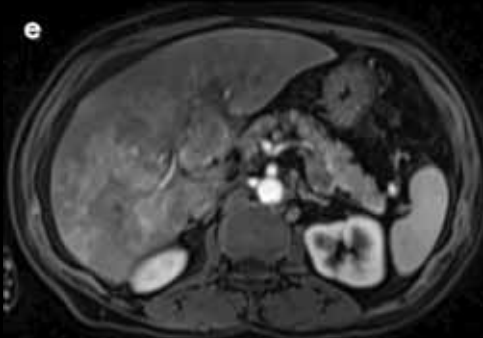
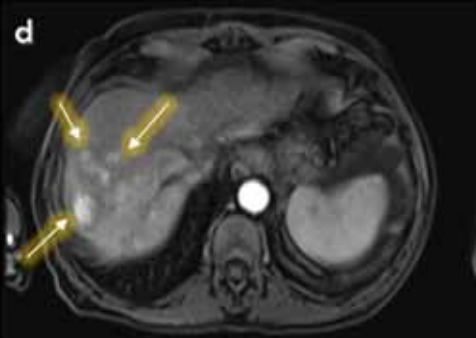
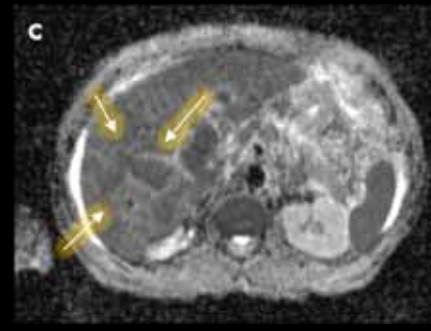
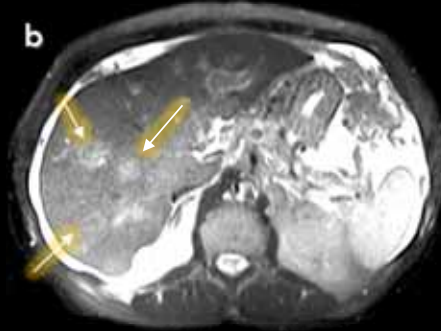
## Atypical Large HCC with PVT



Large HCC with virtually no enhancement in the arterial phase. There is extensive PVT.

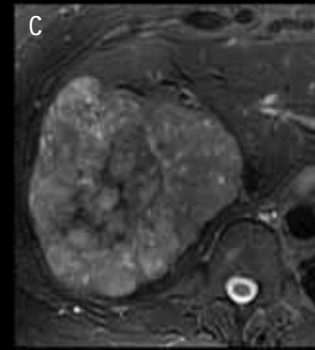
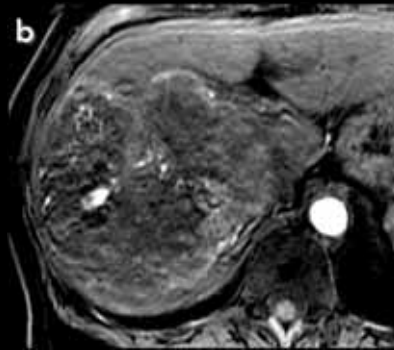
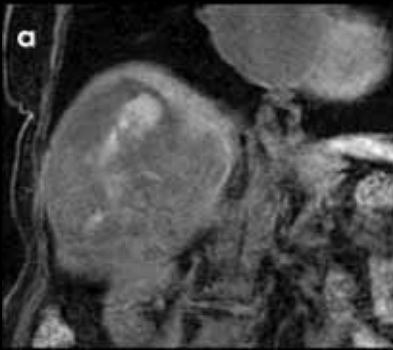


# MR: HCC with PVT

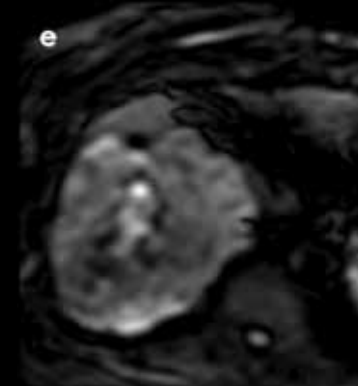


- a) T1W fat suppressed: invisible
- b) T2W: slightly bright
- c) DWI: restricted diffusion and tumor PVT
- d) Arterial: infiltrating HCC, segment 7/8, with enhancing and non-enhancing regions
- e) Late arterial showing extensive PVT

# Large HCC with Hemorrhage Necrosis



- a. T1W: hemorrhage
- b. T2W: mosaic pattern
- c. T2W fat sat: hemosiderin deposit
- d. Post contrast T1: typical capsule and septal enhancement
- e. DWI: susceptibility artifact from hemorrhagic necrosis



## What is the sensitivity and specificity of hepatobiliary imaging combined with contrast-enhanced MR (CEMR) in the diagnosis of HCC?

- Sensitivity: ~75%      Specificity: 95%
- Sensitivity: ~80%      Specificity: 95%
- Sensitivity: ~85%      Specificity: 95%
- Sensitivity: ~90%      Specificity: 95%

- HBP + CEMR is the best detection method for HCC.
  - Gadoxetic acid (a hepatobiliary agent) has a combined sensitivity of 91% and specificity of 95% for cirrhotic and non-cirrhotic livers, even for tumors  $\leq 20$  mm in size<sup>16</sup>.
- MDCT has limited sensitivity (40-78%) but good specificity (93%-99%) for HCC<sup>2,7</sup>.
- CEMR imaging is similar accuracy to CT (sensitivity: 14%-82%, specificity :96-100%)<sup>2</sup>.





# Hepatobiliary Phase (HBP) Imaging

- As HCC tumors progress, they gain a characteristic *hypointense appearance on HBP*<sup>14,17</sup>.
- This is due to decreased expression of organic anion-transporting polypeptide (OATP) in HCC compared to liver parenchyma.
  - Decreases uptake of HBP *intracellular contrast agents*.
- **Considered an ancillary feature in LI-RADS.** Other lesions with similar *hypointense appearance in HBP*<sup>17</sup>:
  - **Hemangioma**: typically show marked hyperintensity on T2W.
  - **Cholangiocarcinoma**: similar in appearance to HCC, but features suggestive of this include target appearance, ductal dilation and lobulated shape.
  - **Dysplastic nodules**: do not usually show arterial phase enhancement.

# HBP and DWI in Prognostication of HCC

- HBP: OATP expression
  - Sometimes, HCC shows HBP hyperintensity. This has a better prognosis<sup>14,18</sup>.
    - Mutation in a signaling pathway leads to overexpression of OATPB13.
    - It is associated with higher histological differentiation and more favorable prognosis than other HCC' s.
- DWI: VEGF expression
  - Vascular endothelial growth factor (VEGF) promotes angiogenesis, and it' s expression is linked to increased responsiveness to sofrinib<sup>19</sup>.
  - Level of VEGF expression is inversely correlated with the ADC value on DWI.

# Atypical Appearance on MR

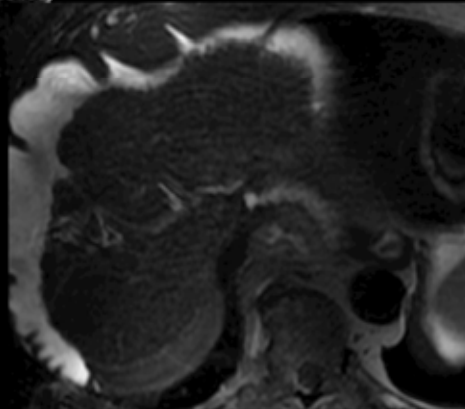


Corona sign in  
early arterial

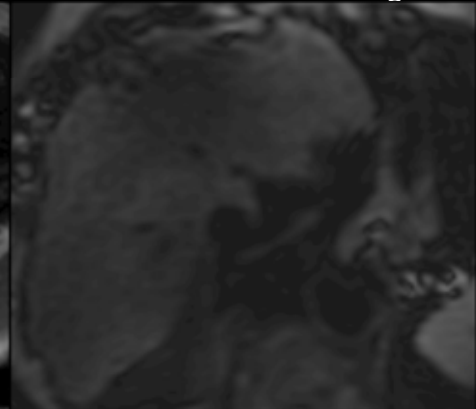


Capsule on late  
arterial/early  
venous

Isointense on T2W



DWI negative



# Small HCC's: A Challenging Diagnosis

Small HCC lesions can be challenging to diagnose because of their atypical features. They fall into 2 general categories<sup>6</sup>

## • Early HCC

- Well differentiated
- Often lack arterial enhancement and washout
- Typically without distinct margins or capsule

## • Small progressed HCC

- Moderate-poorly differentiated
- Only moderately differentiated show arterial enhancement and washout
- Typically with distinct margins, capsule and fibrous septa

The addition of hepatobiliary agents greatly improves sensitivity and specificity for both<sup>16</sup>.

Size threshold for LI-RADS 5 (definitely HCC) is  $\geq 10$  mm, and smaller lesions can be no more than LI-RADS 4.

# Small HCC



Arterial enhancement



No washout

## What is the annual incidence of HCC in patients with NASH?

- <0.5 %
- 1.1 %
- 1.8 %
- 2.6 %
- 3.3 %

- Non-alcoholic fatty liver disease (NAFLD) is on the rise in Western countries, and its end stage variant, non-alcoholic steatohepatitis (NASH) is a risk factor for HCC in patients without cirrhosis.
- The incidence of HCC in patients with NASH is 2.6%. [for comparison, 4% in HCV cirrhosis]<sup>21</sup>.



# HCC in Non-Cirrhotic Livers

- HCC presents at a **later stage in non-cirrhotic patients** who are not screened<sup>23</sup>.
  - 25% present with extra-hepatic metastases.
- HCC's in non-cirrhotic livers tend to be **larger, well-circumscribed, unifocal** and with **capsules** or **small satellite lesions**<sup>24</sup>.
- **Similar percentage of atypical appearance** of HCC between cirrhotic and non-cirrhotic patients<sup>24</sup>.
- In non-cirrhotic livers, presence of central scar and radiating septa are associated with HCC<sup>13,25</sup>.

# Differential for Arterial Enhancing Focal Liver Lesion in the Non-Cirrhotic Liver<sup>26</sup>

- **Focal nodular hyperplasia (FNH)**: strongly enhancing in arterial phase fading to isoenhancing in portal-venous phase. It can contain stellate central scar and is hard to differentiate from HCCs.
  - FNH: **hyper-** or **isointense** on HBP.
  - HCC: *hypointense* on HBP.
- **Hepatocellular adenoma (HA)**: (very rare) weakly enhancing in arterial phase and isoenhancing in portal-venous and delayed phase. *Hypointense* in HBP.
  - HA: **no washout**.
  - HCC: washout more common.
- **Hemangioma**: homogenous enhancement during arterial phase and during portal venous phase.
  - Hemangioma: enhancement **as bright as aorta** and **portal veins**.
  - HCC: **milder** arterial enhancement. **Venous washout**.



# Summary

- HCC can be diagnosed on imaging **without biopsy**.
- Arterial hyper-enhancement and subsequent washout are **specific but not sensitive** for HCC.
- HCC could have **atypical appearance**.
- Ancillary imaging findings improve the diagnostic yield of imaging in HCC.
- HBP imaging with intracellular contrast agents **improve sensitivity of CEMR** in diagnosing HCCs with atypical enhancement patterns, such as small HCCs.
- Imaging features can correlate with underlying genomic changes that **affect prognosis and response to treatment**.