Confidently See the HCC: A Resident’s Guide to the MRI diagnosis of Hepatocellular Carcinoma

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Learning Objectives

At the conclusion of this presentation, the reader will be able to:

- Describe the contrast enhancement patterns of hepatocellular carcinoma (HCC) in dynamic phase and hepatobiliary phase imaging

- Describe imaging features and discuss MRI sequences that may aid in the diagnosis of HCC

- Eliminate confusion regarding the various imaging classification schemes that exists for diagnosing HCC
Hepatocellular carcinoma (HCC) is among the most prevalent solid organ cancers and most common causes of cancer-related mortality.

- Age-standardized incidence rates vary from 2.1 per 100,000 in North America to 80 per 100,000 in China.
- Viral hepatitis and non-alcoholic steatohepatitis are the most common causes of HCC.
- HCC is the only major solid organ malignancy that is diagnosed with imaging criteria.

**Imaging Criteria**

- T2W: Transverse T2-weighted image
- T1W pre: Transverse T1-weighted pre-contrast image
- Arterial: Arterial phase image
- PV: Portal venous phase
- HB: Hepatobiliary phase

*PV= portal venous phase, HB= hepatobiliary phase*
Dysplastic nodules

- Carcinogenesis of HCC occurs in a stepwise fashion, comprising the following steps: dysplastic nodule (DN), low-grade HCC, and high-grade HCC.
- Histologic grade of HCC has shown to be an important prognostic factor for patient outcome.
- Dysplastic nodules are more likely to be brighter in signal on the T1-weighted sequence and darker in signal on the T2-weighted signal compared to HCC.
- High grade dysplastic nodules are considered premalignant, and are difficult to distinguish from HCC on imaging.

The low grade dysplastic nodule appears hyperintense compared to the background liver on the T1 weighted sequence. No enhancement is seen within the arterial or portal venous phase.
Magnetic Resonance Imaging

- **Dynamic Phase Imaging**
  - Pre T1-weighted sequence
  - Arterial phase (~20-30 seconds)
  - Portal venous phase (~60-70 seconds)
  - Delayed Phase (~3 minutes)

- **Hepatobiliary Imaging**
  - ~15-20 minutes post contrast injection (Gd-EOB-DTPA)

- **Ancillary features**
  - T2-weighted sequence
  - Diffusing weighted sequence (DWI)
  - In and Out of Phase
Contrast Agents

- **Extracellular gadolinium contrast agents:**
  - Conventional contrast agent used for MR imaging of the liver
  - Excreted primary through the kidneys
  - Allows dynamic T1-weighted imaging, which includes the arterial, portal venous, and delayed phases

- **Hepatobiliary contrast agents:**
  - Also known as gadolinium-ethoxybenzyl diethylene-triaminepentaaceticacid (Gd-EOB-DTPA)
  - Approved for clinical use in the United States in 2008
  - Has a ratio of 50:50 biliary-renal excretion
  - Biphasic distribution:
    - **Blood Pool phase:** distributes into the extracellular compartment, similar to conventional MRI contrast agents
    - **Hepatocyte phase:** actively taken up by functioning hepatocytes by the OATP receptor
    - Allows for hepatobiliary phase imaging 20 minutes post-injection
    - Has shown to improve the detection and characterization of hepatic lesions, compared to unenhanced MRI and dynamic CT
T1-weighted sequence

- HCC are predominantly hypo or isointense on the T1-weighted sequence.

- Tumors with hemorrhage or fat may be hyperintense in signal on the T1-weighted sequence.

The HCC nodule appears isointense to the background liver on the pre contrast T1 weighted sequence. After administration of contrast, arterial enhancement of the nodule is seen.

The low-grade dysplastic nodule appears hyperintense to the background liver on the pre contrast T1 weighted sequence. No arterial enhancement is seen within this nodule.

The Hepatocellular Carcinoma (HCC) nodule appears isointense to the background liver on the pre contrast T1 weighted sequence. After administration of contrast, arterial enhancement of the nodule is seen.
Arterial Phase

- HCC normally enhances on the arterial phase, appearing hyperintense to the background liver.

- Development of neovascularity seen with HCC is one of the biologic features which separate HCC from benign dysplastic nodules.

The HCC mass appears hypointense to the background liver on the pre contrast T1 weighted sequence. Heterogeneous enhancement of the mass is seen on the arterial phase, and the mass appears to wash out on the delayed phase.
Portal Venous Phase/Delayed Phase

- On the portal venous and delayed phase, HCC appears hypointense to the background liver, also known as “wash out”

- Distinguishing dysplastic nodules and low-grade HCC on imaging may be challenging as low-grade HCC and dysplastic nodules are more likely to maintain portal venous flow compared to high-grade HCC

The HCC mass appears isointense to the background liver on the pre contrast T1 weighted sequence, with evidence of enhancement on the arterial phase, and decreased signal delayed phase.
Hepatobiliary Phase

• The hepatobiliary phase is best evaluated 20 minutes after EOB injection
• HCC shows no uptake of gadolinium EOB DTPA on the hepatocyte phase given lack of functional hepatocytes
• Tumor margins are most clearly delineated in the hepatocyte phase, potentially improving detection of HCCs not readily visible in dynamic imaging phases
• Challenges include detection of very small lesions (<1 cm) and distinguishing premalignant dysplastic nodules from HCC

(A) Segment 2 liver mass demonstrates no gadolinium EOB DTPA uptake on the hepatobiliary phase. The findings from this biopsy disclosed a well–differentiated hepatocellular carcinoma. (B) Segment 7 liver nodule demonstrates gadolinium EOB DTPA uptake on the hepatobiliary phase. Pathology revealed nodular regenerative hyperplasia. Of note, peripheral gadolinium EOB DTPA uptake of the portal venous system is also seen in this patient with sclerosing portal venopathy.
Green HCC

- HCC can produce bile, which changes macroscopically to a green color after fixing with formalin. These tumors are called “green HCC”

- HCC which produce bile may have the receptor for Gd-EOB-DTPA uptake

- HCCs may show paradoxical uptake of Gd-EOB-DTPA and are recognized as iso- or hyperintense lesions in the hepatobiliary phase

- Uptake of Gd-EOB-DTPA has been significantly correlated with “green HCC”

74 year old man with history of hepatitis C cirrhosis was found to have a segment 2 liver mass on dynamic triple phase imaging, and which was given a LIRADS 5B based on its enhancement characteristics. However, the mass demonstrated uptake of gadolinium EOB DTPA on the hepatobiliary phase (red arrow). Pathology revealed this mass to be HCC.
T2-weighted sequence

- T2 hyperintensity refers to signal intensity on T2 weighted images that appears greater than background liver.

- Studies have shown that T2 hyperintensity predicts HCC over dysplastic nodules.

- “Nodule within a nodule”: Dysplastic nodules may dedifferentiate into HCC, with the dysplastic nodule appearing T2 hypointense and the focus of HCC appearing T2 hyperintense.

82 year old woman with hepatitis C cirrhosis. Segment 6 of the liver demonstrates a 4 cm mass (green arrow), which appears T2 hypointense compared to background liver. A focus at T2 hyperintensity (red arrow) is also seen within the T2 hypointense mass. Pathology revealed HCC within a dysplastic nodule.
DWI sequence

• DWI has been shown to provide high conspicuity for infiltrative HCC compared to unenhanced T1 and T2 weighted imaging.

• Tumors are hyperintense on DWI because of increased cellularity of the tumor, preventing free diffusion of water.

• Does not significantly improve diagnostic accuracy in detecting small HCC (<2 cm) or distinguishing malignant from benign portal vein thrombus in cirrhotic patients.

• May be used in treatment monitoring of HCC patients because of its sensitivity for changes in tumor cellularity and cell membrane integrity.

A large liver mass is seen within the left hepatic lobe in a 62 year old man with nonalcoholic fatty liver disease. The mass was hyperintense on the B1000 sequence. Pathology results revealed well-differentiated hepatocellular carcinoma.
Intralesional Fat

- Fat has been shown to be important in differentiating dysplastic nodules from early HCC, with HCC more likely to contain microscopic fat.
- Intralesional fat within HCC can be evaluated on the in and out of phase sequences.

An infiltrative mass that was found to be HCC is present within the left lobe of the liver, which appears to decrease in signal on the out of phase sequence, consistent with microscopic fat. Heterogeneous enhancement of the mass is seen on the arterial phase.
Encapsulation

• Refers to a smooth peripheral rim of enhancement in the portal venous or delayed phase

• Presence of encapsulation of a nodule has been shown to favor HCC in cirrhotic livers, with a positive predictive value up to 95%

• Utility of encapsulation for confident HCC diagnosis remains controversial, as fibrotic tissue may mimic delayed enhancing capsule

70 year old man with nonalcoholic fatty liver disease. A 3 cm lesion is seen in segment 2 of the liver, with smooth peripheral enhancement, that appears most conspicuous on the delayed phase. Findings from this biopsy disclosed a well –differentiated hepatocellular carcinoma.
Size and Growth

• The larger the liver mass, or if a mass demonstrates interval growth, the more likely for the nodule to be HCC
• Some imaging criteria include size and growth as part of their criteria for the diagnosis of HCC, such as the LI-RADS criteria, while others do not, such as the Japan Society of Hepatology
• The definition of growth is dependent on the classification scheme. For example, OPTN requires a >=50% growth in diameter in 6 months to be classified as growth
• Our ability to confidently diagnose HCC in small nodules is much less than for larger nodules
Portal Vein

• When a mass is seen within the liver, comments on the patency of the portal vein should be made on the imaging report.

• Tumor involvement of the portal vein excludes patients from receiving a liver transplant.

• Arterial enhancement within the portal vein thrombus can help differentiate tumor thrombus from bland thrombus.

The liver is cirrhotic with multiple arterially enhancing liver lesions that were found to be HCC (dotted arrow). Infiltrative tumor is seen extending into the right portal vein, which appears thrombosed (solid arrows). A TIPS stent is seen (asterisk).
Imaging Criteria

- American Association for the Study of Liver disease (AASLD)*
- Organ Procurement and Transplant Network (OPTN)*
- Liver Imaging Reporting and Data System (LI-RADS)*
- Japan Society of Hepatology (JSH) *
- European Association for the Study of the Liver (EASL)
- Asian Pacific Association for the Study of the Liver (APASL)

*Will be discussed in this presentation.
AASLD

• The 2010 American Association for Study of Liver Disease (AASLD) criteria is among the most widely utilized imaging criteria for diagnosing HCC

• Size of $\geq 1$ cm, early post contrast arterial enhancement above background and portal venous or delayed phase washout below background is considered diagnostic for HCC

• A subgroup of both dysplastic nodules and HCC lesions may maintain portal venous flow, making differentiation challenging

A mass is seen within the liver that was greater than 1 cm in size, appeared to enhance in the arterial phase, and appeared to wash out in the portal venous phase. This mass was diagnostic for HCC by AASLD criteria, and was found to be HCC on pathology.
• United Network for Organ Sharing (UNOS): administers the OPTN and in charge with fair allocation of livers for transplant

• Criteria for medical urgency are based on the MELD score, which is predictive of the likelihood of death within the next 90 days, with the scores ranging from 6 (less ill) to 40 (gravely ill).

• OPTN/UNOS policy increase priority for candidates with HCC that are within the Milan criteria by assigning a MELD exception score

• Milan Criteria: Three OPTN class 5A or 5B HCCs, each 1 cm or larger and 3 cm or smaller in diameter, or one OPTN class 5B HCC measuring 2 cm or larger and 5 cm or smaller in diameter

http://optn.transplant.hrsa.gov
LI-RADS

- Imaging criteria **supported by the American College of Radiology (ACR)**
- Standardizes the diagnosis of nodules in cirrhotic livers
- **LI-RADS category 5 lesions** are regarded as HCC and undergo definitive treatment without biopsy
- LI-RADS 5 was made to be consistent with OPTN 5 classification scheme
- Only in 2014 has LI-RADS expanded to apply to hepatobiliary contrast agents
  - Lesions cannot to be upgraded to LI-RADS category 5 using this phase

**LI-RADS category 5**
- Arterial enhancement
- Wash out
- Capsule
- >2 cm
LI-RADS v2014

Diagnostic for Hepatocellular Carcinoma

http://www.acr.org/quality-safety/resources/LIRADS
Japan Society of Hepatology (JSH)

- Published imaging criteria for the noninvasive diagnosis of HCC in 2007 and with updates in 2010
- Incorporates the use of the hepatobiliary phase as a major criteria to assist in the diagnosis of nodules in cirrhotic livers
- “Typical HCC” and “HCC” are considered diagnostic for HCC
Liver mass demonstrates enhancement on the arterial phase. However, no washout was seen on the portal venous phase. With the help of the hepatobiliary phase, the mass appeared more conspicuous, and there was a lack of uptake of the hepatobiliary contrast agent. While this mass did not meet the AASLD criteria for HCC since it retained contrast on the portal venous phase, this mass was considered to be diagnostic for HCC based on the JSH criteria. The findings from this biopsy disclosed HCC.
Surgical Treatment

- **Liver Resection:** Only 10–15% of HCC patients are eligible for liver resection due to the severity of underlying cirrhosis or the diffuse distribution of the tumor.

- **Liver transplantation:** This is the best treatment for HCC as it not only removes the tumor, but also removes the remaining diseased liver tissue that is at risk for the development of de novo cancer.

The patient had a history of HCC and had a liver transplant. There is an abrupt cut off the hepatic artery at the anastomosis (arrow), with collateral vessels seen within the liver.
Nonsurgical treatment

- **Tumor ablation (ie. radiofrequency, cryoablation, alcohol):** If patients are not eligible for surgery, they can undergo ablation of their tumor. Local ablation may also be used to control HCC while awaiting transplantation.

- **Chemo or radioembolization:** These transarterial therapies are based on the idea that HCC is supplied mainly by the hepatic artery.

- **Recurrent tumor would have similar features as HCC**

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A patient with history of HCC status post ablation of the tumor with an ablation defect is seen (asterisk). However, there appears to be an enhancing nodule (arrow) just anterior to the ablation defect, concerning for recurrent tumor.
HCC Mimics

- Metastases to the liver are more common than primary tumors.
- Metastases also demonstrate hypoenhancement on the hepatobiliary phase, making it difficult to distinguish from HCC.
- In a patient with a liver mass and cirrhosis, HCC is more likely.
Conclusions

- HCC is the only solid organ malignancy to be diagnosed with MR-based imaging criteria, obviating the need for tissue diagnosis.

- Many classification schemes exist for HCC, and familiarity with these schemes may allow for early diagnosis and initiation of appropriate treatment.
References