MRI ancillary findings on HCC diagnosis

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Learning objectives

- To recognize hemodynamic features that allow for Hepatocellular Carcinoma (HCC) to be confidently diagnosed.
- MRI has the greatest sensitivity and specificity for the diagnosis of HCC.
- To get familiar with and understand the accuracy of different MRI ancillary findings for HCC diagnosis.
Background

HCC is the most common primary malignancy of the liver and the third most common cause of cancer related death. Screening of high-risk patients allows earlier HCC diagnosis, allowing these patients to undergo curative therapies.

Unlike most malignancies, which typically require biopsy for definite diagnosis, HCC can be diagnosed based on CT or MRI characteristics alone due to the high specificity of these modalities.

Several studies have demonstrated a trend to increased sensitivity and specificity of dynamic MRI over dynamic CT for the detection and characterization of HCC of all sizes, with reported overall sensitivities of 77%-100% for MRI and 68%-91% for CT. MRI obtained with up-to-date techniques and in expert hands, reproduce altered hepatic morphology, fibrotic changes and cirrhotic nodules, thereby being the exam of choice for HCC diagnosis.

Actually, most criteria for HCC diagnosis rely on the hemodynamic features of the nodules, i.e. hyperenhancement on the arterial phase and "washout" on the portal or equilibrium phase (fig. 1). These criteria are related to the hemodynamic features of the nodules, attributed to shift in tumor blood supply from predominantly portal venous to predominantly arterial branches recruited during neoangiogenesis.

The capsule appearance (peripheral rim of smooth and progressive enhancement with hyper-enhancement in the portal venous or delayed phase) (fig. 2) is another major feature considered by some guidelines, specifically, Liver imaging Reporting and Data System (LI-RADS) and United Network for Organ Sharing (UNOS). This capsule appearance is characteristic of progressed HCC and is attributed to compressed parenchyma, fibrosis, dilated sinusoids/blood vessels around mass, or a combination of these. In at-risk patients, capsule appearance has high positive predictive value for progressed HCC.

Despite these criteria are almost 100% sensitive for lesions >2cm, their sensitivity drops to about 80% for smaller nodules because of their tendency to have atypical enhancement patterns.

In order to improve MRI accuracy, ancillary features have been described, i.e., imaging features that are not diagnostic but that modify the likelihood of HCC. Presently, LI-RADS, developed by the American College of Radiology (ACR), is the only classification system that applies those features in their criteria. These guidelines classify lesions into five categories ranging from definitely benign to definitely HCC: LR-1 (definitely benign), LR-2 (probably benign), LR-3 (indeterminate probability of HCC), LR-4 (probably HCC), LR-5 (definitely HCC). This probability is given by the combination of major criteria, which favor
benignity or malignancy, and the ancillary imaging features that allows the radiologist to downgrade or upgrade categories (table 1).

Ancillary features can be divided into those favoring diagnosis of benignity and those that favor malignancy, the latter being further categorized as specific or not-specific for HCC.

Our educational exhibit will focus only on ancillary findings that suggest malignancy.

**Features that favor malignancy, specific for HCC**

**Intra-lesional fat**

Fatty metaplasia is frequently histologically observed in early HCC and its detection at imaging favors the diagnosis of HCC. However, it does not establish the diagnosis of HCC, as high-grade and, occasionally, low-grade dysplastic nodules may also show intra-lesional fat. Nevertheless, in a high-risk patient, the identification of intralesional fat in a suspicious nodule raises concern for malignancy or premalignancy, which should prompt, at least, a closer follow-up (fig.3).

Intralesional fat may have value as a prognostic feature since it is characteristic of early but not progressed HCC having more favorable prognosis, with longer time to progression and less risk of developing metastases than non-fat-containing HCCs.

A remarkable point, is that the presence of intra-lesional fat on a single nodule in a cirrhotic liver is characteristic of early HCC, especially if larger than 1.5 cm (fig. 4). On the other hand, it is not specific as low and high-grade dysplastic nodules also may have fat. The presence of numerous fat-containing nodules < 1 cm suggests that these lesions are benign.

The incremental value of this finding for diagnosis of HCC is relatively limited since it often coincide with other more discriminatory imaging features (fig.5).

**Nodule-in-nodule architecture**

This finding represents the emergence of a progressed HCC within a dysplastic nodule (fig.6). The subnodule corresponding to the HCC typically shows enhancement characteristics similar to other HCCs.

It is an uncommonly depicted feature at CT or MRI, hence, incremental value for HCC diagnosis may be modest.
Mosaic architecture

Mosaic architecture refers to the presence of randomly distributed internal compartments differing in enhancement, intensity, shape and size within a mass, often separated by fibrous septations. In high-risk patients, most masses with mosaic architecture are HCCs, being more characteristic of large HCCs.

As it is uncommon in small HCC, the incremental value of this feature for HCC diagnosis may be modest. Nevertheless, this feature may be important for the diagnosis of large hypovascular HCCs (fig.7).

Blood products

The presence of intra-lesional or peri-lesional hemorrhage in the absence of biopsy, trauma or intervention is also an ancillary feature favoring HCC. At MRI, blood products usually manifest as areas predominantly high signal intensity on T1-WI and heterogeneous, predominantly low signal intensity on T2-WI. Due to T2* shortening, there may be signal loss on the second echo of a dual-echo gradient-echo sequence.

Features that favor malignancy, not specific for HCC:

Mild-moderate T2 hyper-intensity

Mild or moderate T2 hyper-intensity comparing to the liver is highly suggestive of malignancy (fig.8). Cirrhotic and dysplastic nodules characteristically are iso or hypointense on T2-weighted images, rarely showing mild/moderate T2 hyperintensity. Thus, mild or moderate hyperintensity in a nodule in a cirrhotic liver is highly suggestive of malignancy, specifically HCC, and it can be useful for differentiation between dysplastic nodules and small HCCs. Mild T2 hyper-intensity is seen in 77% of HCCs larger than 3cm, with many well-differentiated HCCs and some small moderately differentiated HCCs being T2 isointense or hypointense. For that reason, mild T2 hyper-intensity may have prognostic significance.

However, it has low specificity for HCC as other lesions can show mild T2 hyperintensity, as intra-hepatic cholangiocarcinoma (ICC) and metastases.

Restricted diffusion
Diffusion-weighted imaging (DWI) hyperintensity within HCC relative to liver parenchyma is expected due to its highly cellular tissue (fig.9). In contrast, benign nodules usually present a similar microstructure and hence water diffusivity is preserved. Therefore, DWI may be useful in detecting HCC amongst benign nodules and arterially enhancing pseudolesions, predicting the histological grade, and assessing its response to treatment, as treatment-induced necrotic and inflammatory tissues cause reduced cellular density and increased membrane permeability with diminished restriction to diffusion.

However, cirrhotic parenchyma itself also shows restricted diffusivity, presumably owing to the abundance of fibrotic tissue, which results in reduced HCC conspicuity at DWI.

The limitation of this feature is its sensitivity, as many HCCs, especially those lesser than 2 cm in size, do not show restricted diffusion.

One possible pitfall for this feature are small hemangiomas, which may have high signal intensity on DWI and be mistaken for HCC. To overcome this pitfall other characteristics, especially T2 hyperintensity and dynamic behavior of the nodule may allow the correct diagnosis.

**Hepatocyte-Specific/ Hepatobiliary Contrast Agents (HSA)**

HSA - Gadoxetic acid disodium (Eovist®/Primovist®; Bayer Healthcare) and gadobenate dimeglumine (MultiHance®; Bracco Diagnostics) - have been increasingly recognized as an important tool for HCC diagnosis. Only normal functioning hepatocytes take up HSA and excrete them to the biliary tree due to the action of cellular membrane transporters named Organic Anionic Transporting Polypeptides (OATP) and Multidrug Resistance-associated Proteins (MRPs). Because expression of these transporters decreases during hepatocarcinogenesis, low SI on HBP images is a strong predictor of premalignancy or malignancy (high-grade DNs or HCCs), while iso SI to high SI on HBP images is generally suggestive of benign lesions (RNs or low-grade DNs).

One important benefit of the hepatobiliary phase is that it helps to distinguish arterially enhancing pseudo-lesions (such as arterio-portal shunts) from HCC and identify early HCCs, which are frequently isoenhancing in the vascular phases and so cannot be reliably detected with extracellular agents (fig.10 and 11).

However, approximately 10% of HCC's show high SI on HBP images. These, usually represent well-differentiated HCCs that may retain enough hepatocellular and OATP expression allowing the uptake of hepatobiliary-specific agents.

Advanced cirrhosis may also limit gadoxetic acid-enhanced MRI in the detection of early HCC because of compromised uptake of hepatobiliary-specific agents by
damaged hepatocytes, resulting in decreased distinction between the background liver parenchyma and the lesion.

Lesional fat sparing

In patients at risk for HCC whom have fatty liver infiltration, if a suspicious lesion has lower fractional fat content than background liver, it is an ancillary feature favoring HCC. It must be differentiated from hepatic fat sparing areas, by confirming the different enhancement pattern from that of background liver. This is easily performed using subtraction technique.

Lesional iron sparing

As with lesional fat-sparing, the absence of iron deposition in a suspicious lesion within an iron-overloaded liver parenchyma is highly suggestive of premalignancy or malignancy, as high-grade dysplastic nodules and HCCs cells lose the ability to concentrate iron (fig.12).

Liver iron deposition can be shown as signal loss on the second echo of a dual-echo sequence or as abnormal hypointensity on T2- or T2*-weighted images.

A limitation is that it is applicable only to solid nodules in iron-overloaded livers. Another limitation is that this feature is not specific for HCC as it also is observed in other malignancies, such as with intra-hepatic cholangiocarcinoma or confluent fibrosis.

Corona enhancement (perilesional enhancement)

Is defined as a rim of perilesional enhancement that is seen in hypervascular and progressed HCC in the late arterial or early portal venous phase, which fades to isoenhancement in the portal venous phase or delayed phase (fig.13). It corresponds to rapid dissipation of contrast material from the arterially hyperenhancing mass to the peritumoral parenchyma, carried by the tumor draining vessels, just a few seconds after the tumor itself begins to enhance. Corona enhancement is not specific to HCC as other hypervascular tumors such as metastasis can also have that feature. However, its presence may help in distinguishing between HCC and vascular pseudolesions (e.g., arterio-portal shunt).

This feature may also have some prognostic value as it is not usually present on early HCC, but on less differentiated lesions.
Diameter increase less than threshold growth:

A diameter increase less than the defined threshold growth for a major feature (LI-RADS classification) (fig.14) is also considered an ancillary feature that favors HCC. That is to say:

- diameter increase less than 5mm
- diameter increase <50% over $\leq 6$ months
- diameter increase <100% over >6 months
- new mass measuring <10mm, regardless of the time interval.
Fig. 1: Typical HCC findings on dynamic MRI study: this example shows the classical MRI findings of HCC: hyperenhancement on the arterial phase and "washout" on the portal or equilibrium phase. It is also shown the capsule appearance, i.e. peripheral rim of smooth and progressive enhancement with hyper-enhancement in the portal venous or delayed phase.

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Fig. 2: Late capsular enhancement: In this case, there is a hypervascular lesion which is mild hyperintense in T2-WI, shows hyperenhancement on arterial phase but does not washout on the interstitial phase. Nevertheless, a capsule appearance is depicted in the interstitial phase. In at-risk patients, this finding has high positive predictive value for HCC. The pathologic exam was compatible with HCC.

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<table>
<thead>
<tr>
<th>LR-1 Definitely Benign</th>
<th>100% certainty observation is benign.</th>
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<tbody>
<tr>
<td>LR-2 Probably Benign</td>
<td>High probability observation is benign.</td>
</tr>
<tr>
<td>LR-3 Intermediate probability for HCC</td>
<td>Both HCC and benign entity have moderate probability.</td>
</tr>
<tr>
<td>LR-4 Probably HCC</td>
<td>High probability observation is HCC but there is not 100% certainty.</td>
</tr>
<tr>
<td>LR 5 Definitely HCC</td>
<td>100% certainty observation is HCC.</td>
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**Table 1:** LI-RADS - this reporting system evaluates liver lesions for HCC probability, based on classical HCC features and other ancillary findings. (adapted from Liver Imaging Reporting and Data System (LI-RADS) 2014 by American College of Radiology).

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**Fig. 3:** Intra-lesional fat: this case demonstrates a 8 mm nodule which shows signal loss from the IP to the OP sequence and that is hypointense in the fat-suppressed sequences, compatible with intralesional fat. On dynamic study, its hypervascular nature is obscured by its basal hipointensity, however it was confirmed on subtracted images. This nodule shows washout, thus being extremelly suspicious for HCC despite its small size.

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**Fig. 4:** Intra-lesional fat: this case demonstrates a nodule which shows signal loss from the IP to the OP sequence and that is hypointense in the fat-suppressed sequences, compatible with intralesional fat. On the dynamic study, its hypervascular nature is obscured by its basal hipointensity, however it was confirmed on subtracted images (lower right).

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**Fig. 5:** Intra-lesional fat: this case demonstrates a nodule in a cirrhotic liver, which shows signal loss from the IP to the OP sequence and that is hypointense in the fat-suppressed sequences, compatible with intralesional microscopic and macroscopic fat. On the dynamic study, its hypervascular nature is partly obscured by its basal hipointensity, however showing evident wash-out on interstitial phase, diagnostic of HCC.

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**Fig. 6:** Nodule-in-nodule architecture: in segment VI, there is a nodule without major features of HCC. Inside that nodule a smaller nodule is identified (red arrow), which shows mild high T2 signal intensity, arterial hyperenhancement and delayed washout in comparison with the background liver parenchyma. This appearance of nodule inside another nodule in an at-risk patient is highly suggestive of HCC.

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Fig. 7: Mosaic architecture - in this patient with chronic liver disease, a mass is depicted. Within the mass, randomly distributed internal compartments are depicted on T2-weighted images consistent with mosaic architecture. This mass is hypovascular with heterogeneous appearance. Despite not having typical dynamic features of HCC, the presence of this ancillary finding is highly suggestive of HCC.

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**Fig. 8:** Mild T2 hyper-intensity: in this patient with chronic liver disease, a nodule is depicted showing arterial hyperenhancement without washout on later phase images. It showed mild hyperintensity on T2-weighted images, better depicted on fat-suppressed images. This finding in an at-risk patient is suggestive of malignancy. Biopsy revealed HCC.

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**Fig. 9:** Restricted diffusion: In this patient with chronic liver disease, a small nodule is depicted, showing mild hyperintensity on T2-weighted images, arterial hyperenhancement, without clear washout on venous phase. In DWI, restriction to diffusion is noted, suspicious for malignancy.
**Fig. 10:** Low signal intensity on biliary phase with Hepatobiliary Contrast Agents: A lesion is seen in the caudate lobe, showing mild hyperintensity on T2-weighted images, with subtle arterial hyperenhancement and washout on venous phase. Its low signal intensity on biliary phase is synonym of lack of functioning hepatocytes, in this case diagnostic for HCC.
**Fig. 11:** Low signal intensity on biliary phase with Hepatobiliary Contrast Agents - it is shown a hypervascular nodule without clear washout on the venous phase. However the presence of capsule and its low signal intensity on biliary phase (lower right) are a strong predictor of premalignancy or malignancy, as expression of normal transporters decreases during hepatocarcinogenesis.

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**Fig. 12:** Lesional iron sparing - in a liver with severe iron deposition, there is an iron-spared nodule. In an high-risk patient, it is an ancillary feature favoring HCC, as high-grade dysplastic nodules and HCCs cells lose the ability to concentrate iron. However, this feature is not specific as it also is observed in other non-HCC malignancies (eg. ICC).

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Fig. 13: Corona enhancement (perilesional enhancement) - there is a nodule with moderate high signal on T2-weighted images, with arterial hyperenhancement but without washout on venous phase. However a rim of perilesional enhancement is seen in the arterial phase, fading on later phases, corresponding to dissipation of contrast material from the arterially hyperenhancing mass to the peritumoral parenchyma. A pseudo-capsule appearance was also depicted. Corona enhancement is not specific to HCC as other hypervascular tumors such as metastasis can also have that feature.

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Fig. 14: Threshold growth: in this example, a small hypervascular nodule was depicted (upper images), not showing other typical features of HCC. On re-evaluation 9 months later (lower images), a dimensional increase was noticed, turning this nodule suspicious for malignancy. In this follow-up exam, washout was also noticed, raising the suspicious for HCC.

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Findings and procedure details

The authors will review the different MRI ancillary findings for HCC diagnosis; discuss their accuracy and illustrate situations where these findings may be important to reach the correct diagnosis.
Conclusion

MRI ancillary findings increase the sensitivity for the diagnosis of HCC and aid radiologists to be more confident about their diagnosis when other major findings do not allow a secure diagnosis of HCC. Ancillary findings should be used while classifying the probability of HCC based on LI-RADS guidelines.
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