13 MRI for Detection and Evaluation of Hepatocellular Carcinoma

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CONTENTS

ABSTRACT

MRI is a useful method of imaging the cirrhotic liver, including for detection and evaluation of hepatocellular carcinoma (HCC), both for its initial diagnosis and following its response to management. In this chapter, we discuss features which allow distinction of HCC from other lesions in the cirrhotic liver, such as regenerative nodules, confluent fibrosis, and benign enhancing pseudonodules. One major strength of MRI is its use of multiple pulse sequences, analogous to the use of various stains for histopathology. Pulse sequences with unique value for characterizing focal liver lesions include T1-weighted, T2-weighted, lipid-sensitive, and multiphasic contrast-enhanced images. Features that facilitate diagnosis of HCC include its shape, capsule, internal nodularity, signal intensity, and sequential

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pattern of dynamic contrast enhancement. It is particularly important that radiologists and clinicians reach understanding on terminology for expressing confidence that a given focal lesion is HCC or benign, so that reported findings are most useful for guiding management decisions. A suggested framework for categorizing this confidence is provided.

Key Words: MRI; liver; hepatocellular carcinoma

Evaluation and management of patients with cirrhosis present many challenges, one of which is the reliable detection of hepatocellular carcinoma (HCC) at a stage when treatment can improve the length and quality of a patient's life. As with other cancers, the potential value of imaging for initial detection depends on many factors, which are the following:

1. Is there a population of high-risk individuals who can be identified for screening by imaging?
2. Is imaging capable of detecting the malignancy earlier than clinical or laboratory methods?
3. Is there an effective method for treating the malignancy at the stage when it is most likely to be detected?
4. Do the benefits of early detection and treatment compare favorably with the financial and other costs of the imaging screening program?

In the case of HCC, the answers to all of the above questions are yes. Patients with cirrhosis, especially of viral etiology, are at high risk for developing HCC *(1–4)*. Magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound can all detect HCC, often before α-fetoprotein and other nonimaging signs allow its diagnosis *(5–9)*. Imaging can be used judiciously to diagnose small HCC, obviating biopsy when imaging diagnostic signs are particularly compelling *(10)*. HCC can be locally treated by many methods, often improved when used in combinations, including chemoembolization, radioembolization, chemical ablations (e.g., ethanol or acetic acid), and RF ablation *(4*, *9*, *11–17)*. The success of these methods might possibly be further augmented when combined with systemic therapy, such as with agents that target VEGF receptors and tumor-induced angiogenesis *(18–20)*. If the local and systemic treatments mentioned above can prevent or prolong the interval before HCC spreads to extrahepatic sites, liver transplant can be used to cure the patient of HCC and prevent recurrence *(11*, *21–25)*. Therefore, HCC presents itself as a particularly valuable opportunity for imaging to improve the lives of patients at risk for this malignancy *(2)*.

In this chapter, I will make some general comments about the challenges that must be addressed to detect HCC within a cirrhotic liver. I will provide a

framework to reduce some confusion regarding terminology that may appear in the imaging literature and in clinical imaging reports. I will then discuss several of the features that help distinguish HCC from other focal findings in cirrhotic livers. Finally, based upon limited literature and some perspective gained from clinical experience, I will offer some suggestions about how the use of MRI for detecting hepatocellular cancer may proceed during the next few years.

1. FOCAL IMAGING FINDINGS IN CIRRHOTIC LIVER

As cirrhosis develops and progresses, the remaining liver parenchyma consists of regenerative nodules of variable size, surrounded by fibrous septations. The first step in evaluating images of a cirrhotic liver is the recognition that the tissue between the fibrotic septations, that is, the regenerative nodules, should generally resemble healthy hepatocellular parenchyma. The abnormal appearance of a cirrhotic liver is caused by alterations in shape due to the combination of scarring, atrophy of some portions, and hypertrophy of others, as well as abnormal signal imparted by the presence of fibrosis and inflammation.

Once a focal part of the liver is noted that appears different compared with the surrounding liver, the next task is to determine whether this tissue is more or less abnormal than the remaining liver parenchyma *(26)*. For example, a relatively sparred area within a severely diseased liver can resemble a mass, when in fact the focal finding is less diseased than the surrounding tissue. The challenge here, before even considering whether there is evidence of malignancy, is to categorize the following benign tissues:

1. *Regenerative nodules*. In fact, the entire cirrhotic liver consists of regenerative nodules. Therefore, any distinct nodule that looks different from the background liver should arouse at least a modest level of suspicion.
2. Confluent fibrosis and severely damaged liver, containing few if any hepatocytes, will look distinctly different from healthy liver parenchyma. Confluent fibrosis is darker on T1-weighted images and brighter on T2-weighted images, features shared by most malignancies, including some HCCs. Confluent fibrosis is therefore best distinguished from HCC by its shape, which is geographic rather round, and by retraction of liver shape, rather than expansion *(27)*.
3. Benign enhancing pseudonodules are the most common problem leading to false-positive diagnosis and frequent follow-up imaging examinations. As discussed toward the end of this chapter, subcentimeter

foci of transient enhancement are extremely common in a cirrhotic liver and are usually benign *(28–32)*. Frequent short-term follow-up of these common benign findings therefore threatens to dramatically increase the overall cost of an imaging screening program, and should be minimized to whatever extent possible *(33)*.

4. Hyperplastic nodule has only scant description in the literature *(34–39)*, although it is probably a common cause of false-positive MRI. Like the more common regenerative nodule, a hyperplastic nodule is composed entirely of benign liver tissue. In fact, there is often minimal distinction between these two entities in the pathologic literature, due to their absence of dysplastic or neoplastic cellular features *(40)*. The main distinction between these two nodular entities is their blood supply, which causes dramatic differences on contrast-enhanced imaging studies but may have little or no effect on their light microscopic appearance. Hyperplastic nodules are thought to arise as a response to alterations in portal venous perfusion, giving rise to nodular hypertrophic tissue with vascular supply entirely from hepatic arteries, without meaningful contribution from portal veins *(41)*. Hyperplastic nodules are most common in the setting of Budd-Chiari syndrome but can arise in any scenario where portal venous perfusion is abnormal, including in patients with cirrhosis. In the setting of an otherwise normal liver, these nodules are termed focal nodular hyperplasia (FNH). In fact, in patients with Budd-Chiari syndrome or cirrhosis, the term "FNH-like nodule" has been used *(35–37)*. This is an unnecessarily redundant term, so the more generic and simpler term hyperplastic nodule is preferable. Hyperplastic nodules are considered entirely benign, without premalignant nature, and should not be confused with dysplastic nodule.
5. Dysplastic nodule is a borderline lesion, with atypical cellular features different from those of regenerative or hyperplastic nodules but not meeting criteria for overt malignancy *(40*, *42*, *43)*. They are considered premalignant, and foci of HCC may develop within them. Dysplastic nodules can be visible on imaging studies, although their features overlap those of some regenerative nodules and some HCCs. Therefore, dysplastic nodule can be included in the differential diagnosis of a nodule in a cirrhotic liver, but at this point, dysplastic nodule is not a specific diagnosis that can be offered by imaging.

HCC is the subject of this entire book and need not be defined here. Rather, in the next section I will describe imaging features of HCC and indicate how these may be used to distinguish them from other nodules and focal findings in the cirrhotic liver.

2. MRI: PULSE SEQUENCES AND GENERAL CONSIDERATIONS

Like other methods of imaging, MRI can depict hepatic and abdominal anatomy. However, MRI also offers a more robust and comprehensive set of tools for characterizing tissue. It is therefore customary for most MRI exams, particularly hepatic MRI, to include multiple pulse sequences repetitively interrogating the same tissue, often in identical image planes. In this respect it is analogous to light microscopy, where the same histologic structure is repeatedly evaluated using different stains, each designed to highlight a particular tissue component of interest. Most MRI examinations will include the following.

2.1. Survey Images

These typically include coronal images but may also include sagittal and transverse images. They provide a brief survey of the abdomen in 1 minute or less and help determine the region of the abdomen to be included in the remainder of the examinations. On occasion, the position of the patient and local receiver coils may need to be changed to best optimize the signals received.

2.2. T1-Weighted Images with Lipid and Iron Sensitivity

T1 is a characteristic of tissues, whereby short T1 leads to high signal intensity (bright on the images) on T1-weighted images. In order of increasing T1 (decreasing brightness on T1-weighted images) are adipose tissue, liver parenchyma, most other tissues including malignancies, and simple cysts. On basic T1-weighted images, adipose tissue is therefore bright, liver medium, and simple cysts dark. HCC has variable appearance and therefore can be dark, intermediate, or bright on T1-weighted images *(44*, *45)*.

Inherent differences between the protons in water and the protons in lipid can be exploited, in various ways, to separate the signals from water vs. lipid protons. It is now routine to obtain T1-weighted images as a pair of images, based on two consecutive echoes *(46–48)*. One of these is "in-phase," where the signals of water and lipid protons add together. The other is "opposed-phase," whereby water protons and most protons from lipid interfere destructively, so that points in the image that contain water and fat, such as fatty liver parenchyma, show up as darker compared with in-phase images. These two paired images, obtained at exactly the same time and place, can either be visually compared or be postprocessed to generate difference images. It is also standard, at some point in the examination, to obtain T1-weighted images where lipid protons are selectively suppressed, generating "fat-suppressed T1-weighted images."

2.3. T2-Weighted Images

These images accentuate differences in the T2 between different tissues. Like T1, T2 is characteristic of tissues. T1 and T2 commonly, but not always, parallel each other. For example, both simple cysts and cerebral spinal fluid have extremely long T1 and long T2, and are therefore bright on T2-weighted images. Liver is dark on most T2-weighted images, whereas moderately to poorly differentiated HCC is usually brighter on these images, similar to spleen. Images can be made more T2 weighted by lengthening the echo time (TE). It is common to obtain two different sets of T2-weighted images, one with moderate T2 weighting to show liver tumors and enlarged lymph nodes, and one with heavy T2 weighting to show fluid as much brighter than solid tissue. In fact, extremely heavily T2-weighted images are commonly obtained to accentuate biliary and pancreatic ducts to form magnetic resonance cholangiopancreatography (MRCP) images. Heavily T2-weighted images are helpful for distinguishing benign cysts and hemangiomas from solid tissue, including HCCs.

2.4. Dynamic Multiphasic Contrast-Enhanced Images

These images are routine and considered essential for sensitive detection of HCC. As a minimum, four separate sets of T1-weighted images, usually with fat suppressed 3D thin-slice technique, are obtained. These included unenhanced images, images obtained during the first pass of contrast material through arteries (arterial phase), images obtained about 20 seconds after the arterial phase (blood pool or venous phase), and images obtained three or more minutes after contrast material has been allowed to equilibrate throughout the vascular and interstitial spaces (delayed or extracellular phase images).

Most HCCs will be bright on arterial phase images due to their predominant supply by arterial rather than portal venous perfusion, and most will be less intense blood pool or delayed phase images (probably because of less fibrosis in HCC compared with background liver parenchyma).

There is a new class of gadolinium contrast agent that has partial hepatobiliary excretion, including gadobenate dimeglumine and gadoxetic acid disodium *(49–51)*. These agents have weak binding to serum proteins, approximately doubling their effect on MR images at a given dose. An additional advantage of these agents is increased enhancement of liver tissue compared with most tumors during delayed phase imaging, after contrast agent has been primarily cleared from blood.

There are some additional images that are included in some protocols because of their potential to provide additive value or confirmation of information from other sequences, but are not necessarily routine.

Diffusion weighted images utilize microscopic water motion to highlight differences between tissues *(52–57)*. Generally, malignant tumors have

restricted water motion compared with many benign tissues. *MR spectroscopy* allows detailed analysis of chemical differences depending on molecular structure, either of protons or other nuclei, but usually with much lower spatial resolution *(58)*. At the present time, neither of these techniques should be considered routine or essential for detecting HCC.

Bright-blood images can be used to demonstrate blood vessels, using either motion-compensated techniques to show the water in blood or use the motion of the blood to show patent vessels. These images are often included if the contrast-enhanced images are technically inadequate due to motion or other artifacts, or if gadolinium contrast agent is not given.

Perfusion imaging. Advances in MRI hardware and pulse sequence design as well as image postprocessing can extend the value of dynamic contrast enhancement so that images are repeated at more rapid intervals. As a first step, early and late arterial phase images can be obtained during one breath hold. Further increases in speed are also possible, and signal intensities at various phases can be measured and applied to various perfusion algorithms to further characterize tissue. The broad class of perfusion imaging has been used to characterize properties of angiogenesis. It is possible that this method of image analysis may prove useful for characterizing response to new treatments such as VEGF antagonists *(18*, *57*, *59–62)*.

Particulate contrast agents. This class of contrast agent, usually consisting of iron oxide particles that accumulate avidly in Kupffer cells and other cells of the reticuloendothelial system, can darken the surrounding liver and thereby improve the visibility of HCC on appropriate MR images *(11*, *21*, *24*, *25*, *63–65)*. The most successful use of iron oxide contrast agents is in "double contrast MRI" when combined with gadolinium contrast agents *(66–71)*. The increased cost of using two contrast agents has prevented adoption of this technique at most centers.

3. CHARACTERISTICS OF HCC

On *T1-weighted MR images*, HCCs can be dark, intermediate, or bright relative to background liver parenchyma. In spite of this extreme variability, T1-weighted images are still useful. For example, hemangiomas, cysts, and most other malignancies are more consistently dark on T1-weighted images, so intermediate or high signal helps to exclude these alternative diagnoses. Comparison of in-phase and opposed-phase images allows detection of even small quantities of lipid, a common finding in HCCs but not present in liver masses that are not derived from hepatocytes, such as hemangiomas, metastases, or cholangiocarcinoma. High signal intensity on both in-phase and opposed-phase images indicates hepatocellular tissue with copper *(72–74)*. These nodules may be HCC, dysplastic nodule, or other liver tissues with cholestasis.

T2-weighted images are often useful for depicting malignant liver tumors as brighter than background liver, although many HCCs have low signal intensity or be invisible on T2-weighted images *(75)*. The main value of T2-weighted images for evaluating suspected HCC is their specificity. A solid round mass in a cirrhotic liver with high signal intensity on T2-weighted images is usually HCC.

The *shape* of a focal liver abnormality is quite helpful. HCCs are usually round, ovoid, or lobulated. HCCs can produce geographic abnormalities after they invade portal veins and disseminate by a portal venous spread.

A *capsule or pseudocapsule* is a common finding surrounding hepatocellular cancer. A capsule appearance is generally not seen with other focal liver lesions such as dysplastic nodule, hydroplastic nodule, or adenoma.

Internal nodularity (mosaic appearance) is a characteristic of HCC caused by variable dedifferentiation of foci within a dysplastic or a neoplastic mass *(76)*. Benign entities such as dysplastic or hyperplastic nodule or liver regeneration have simpler texture, without internal nodularity. At an early stage, a "nodule-in-nodule" configuration results from focal dedifferentiation to HCC within a dysplastic nodule *(42, 77–79)*. A similar appearance can result from focal further dedifferentiation into less differentiated carcinoma within a well-differentiated carcinoma. Therefore, one or more nodules within a focal mass are a strong characteristic of HCC. These focal dedifferentiated nodules will usually have higher signal on T2-weighted images, lower signal on T1-weighted images, and more arterial vascularity. They will also tend to have rounder shape, as they exert mass effect on the less rapidly growing more differentiated remainder of the tumor.

The *dynamic contrast-enhanced series* is the single most important part of an MRI examination for HCC. The characteristics of the dynamic contrast MRI series are in many respects mimicked by dynamic multiphasic CT. One important advantage of MRI over CT is the complimentary value afforded by the additional MRI pulse sequences, which do not have analogous CT counterparts. Additionally, MRI spares the patient repeated exposures to ionizing radiation and iodinated contrast material.

The arterial phase images are the single most sensitive series for detecting HCC. However, there are caveats. While this series may be more sensitive than any single other series, there are indeed HCCs that may be visible only on other pulse sequences, not on arterial phase images *(31, 80)*. Additionally, benign nodules are often seen as hyperintense on arterial phase MR images. In fact, more than 90% of small nodules seen only on arterial phase images are benign *(29, 30, 81)*. The specificity of dynamic contrast-enhanced series is improved greatly if the nodule is visible on at least one additional series. Most commonly, this will be a "washout appearance," whereby a nodule that is hyperintense on arterial phase images is hypointense on blood pool (portal venous) phase or delayed phase images. Additionally, a nodule that is visible on an unenhanced image and then shows increased enhancement relative to

liver during the arterial phase is more likely to be malignant than a nodule that is visible only on arterial phase images *(31)*.

Three illustrative cases are provided in Figs. 1, 2 and 3.

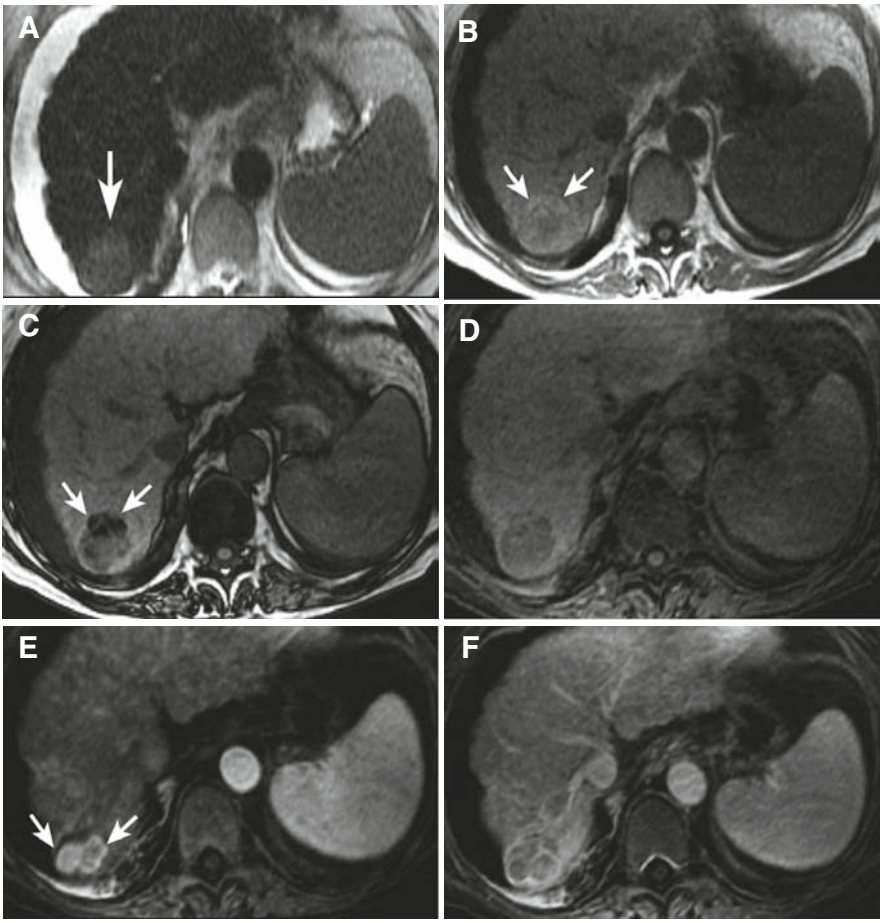

Fig. 1. HCC with many typical MRI features. **A**. T2-weighted image shows HCC as high signal intensity (*arrow*). **B**. T1-weighted image in-phase (water plus fat) shows that most of HCC has similar intensity to remainder of liver, other than increased signal of anterior crescentic portion (*arrows*). **C**. T1-weighted image opposed-phase (water–fat cancellation) shows that HCC lost signal relative to other tissues, indicating lipid content. The anterior crescentic portion (*arrows*) has highest fat content and has therefore lost the most signal. **D**. T1-weighted fat-suppressed image shows the HCC as less signal than the remainder of liver. **E**. As in D, immediately after intravenous injection of gadolinium contrast agent. Hypervascular nodules within the HCC show strong enhancement (*arrows*). **F**. As in E, about 1 minute later. The HCC is now less intense than liver, with a multinodular appearance.

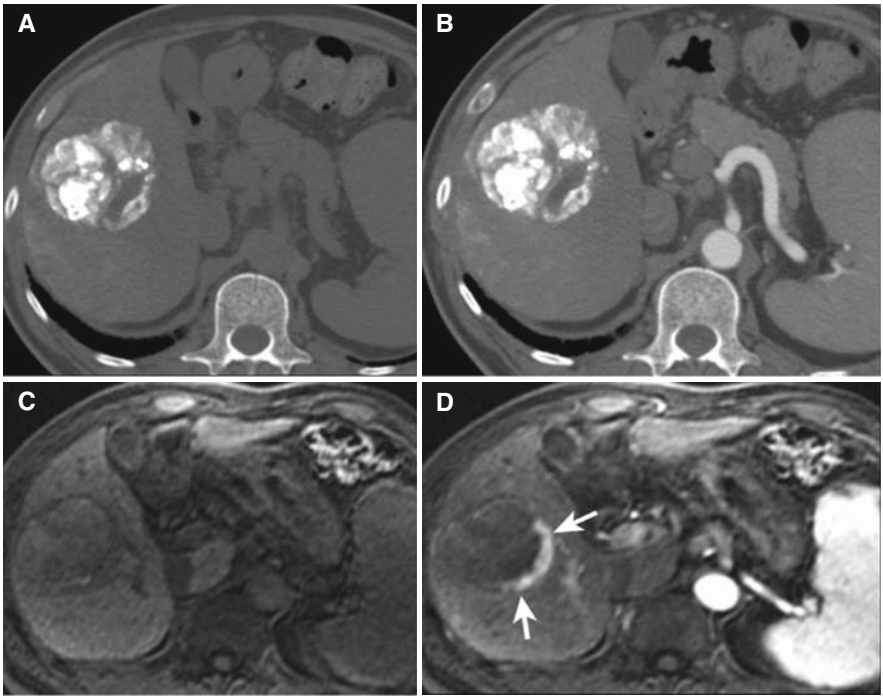

Fig. 2. HCC following chemoembolization, with small remaining viable portion. **A**. Unenhanced CT shows embolic material within HCC. **B**. Contrast-enhanced CT does not show any visible enhancement of tumor. **C**. Unenhanced MRI shows that HCC is of similar intensity to liver. **D**. Arterial phase MRI shows viable hypervascular tissue at the periphery of HCC (*arrows*).

4. REPORTING FINDINGS SUSPICIOUS FOR HCC

The success of screening for HCC depends on detecting the tumor while it can still be treated, without resulting in a frequency of false-negative results that could undermine funding or compliance. Thus far, there is no sufficient data to determine whether repeated imaging at 6-month intervals is superior to annual imaging *(82, 83)*. Our approach has been to attempt confident noninvasive diagnosis with high accuracy while minimizing the frequency of "overdiagnosis" of benign enhancing lesions as HCC. A recent study at our center confirmed that small HCCs that were initially diagnosed as probably benign did not progress to untreatable HCC if a patient adhered to an annual surveillance program *(33)*. To maximize the utility of an MRI-based screening program for HCC among high-risk individuals, we recommend use of the following overall categories for reporting suspicion of HCC.

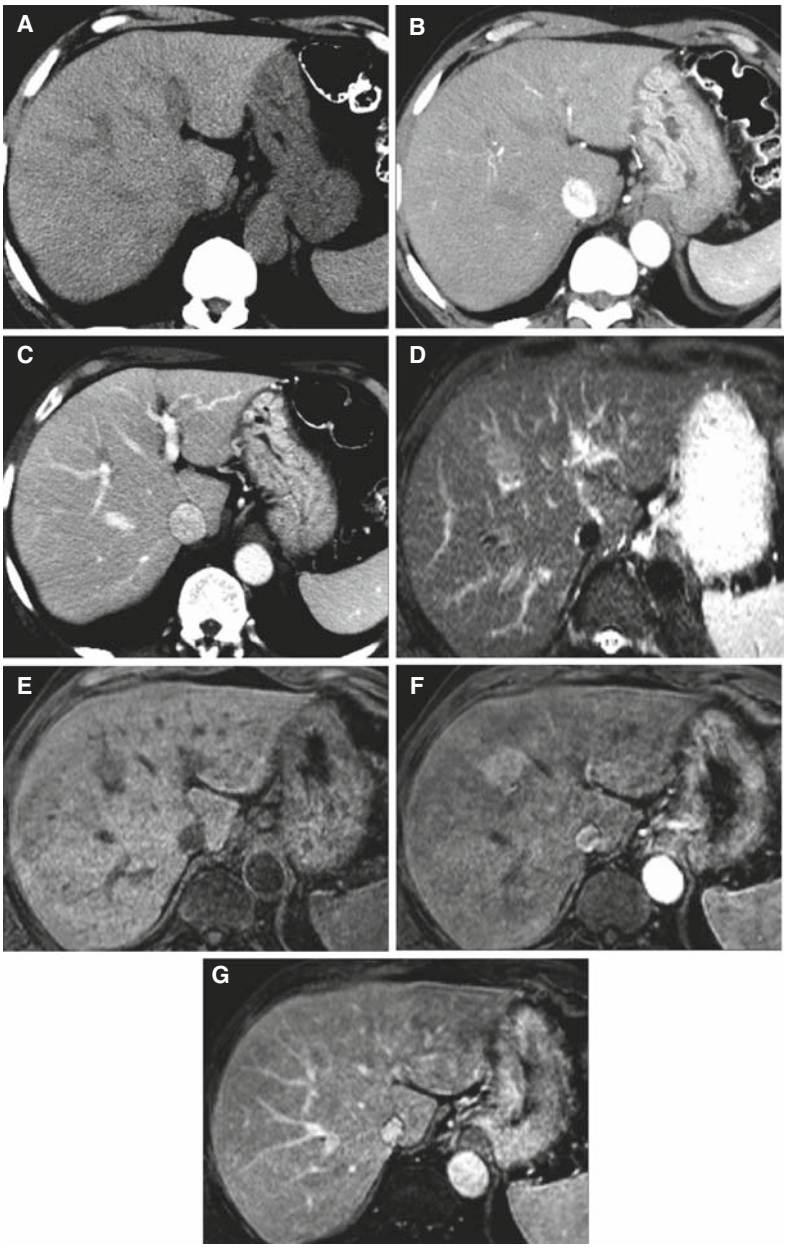

Fig. 3. HCC visible by MRI but not three-phase CT. **A**–**C**. CT images prior to and during arterial and venous phases of contrast enhancement. **D**. T2-weighted MR image shows hyperintense HCC. **E**. T1-weighted MR image shows hypointense HCC. **F**. As in E, immediately after gadolinium contrast agent administration shows moderately hypervascular HCC. **G**. As in E, about 1 minute after gadolinium contrast agent administration does not show the HCC, similar to CT.

4.1. No Nodule with High Suspicion of HCC

These are patients with hepatitis C or other clinical condition that renders them of high risk for developing HCC. This is not changed if low probability lesions, such as subcentimeter foci of transient enhancement, are present. These patients should have repeated examinations at regular intervals, although we are not aware of any data to establish whether 6-month or 12-month intervals are preferable. Although a small minority of subcentimeter transiently enhancing foci may indeed be HCC, well over 90% are benign. If each of these low probability foci triggers a short-term follow-up examination, the overall cost of the screening program may increase geometrically. It is also likely that increasing the frequency of short-term follow-ups may adversely affect overall execution and compliance with the screening program. We therefore recommend that "over-calling" tiny enhancing foci be minimized, provided that these patients are still imaged with a frequency of at least one MRI examination per year *(33)*.

4.2. Indeterminate Nodule

These are usually nodules larger than 1 cm, or other imaging characteristic to generate more than a low probability level of confidence. A diameter of greater than 1 cm is important for two separate reasons. Benign enhancing nodules are usually less than 1 cm in diameter, so larger size by itself raises the possibility of HCC. Additionally, the danger of "under-calling" lesions larger than 1 cm is that tumor doubling will have a more adverse affect if the nodule is already greater than 1 cm. The goal of a screening program is to detect a nodule while it still can be treated optimally. As a mass exceeds 2 cm and becomes progressively larger, the possibility of unsuccessful treatment increases.

An indeterminate nodule will usually trigger a short-term follow-up. The recommended interval will depend on the level of concern regarding rapid interval growth. Typically, the interval recommended will be between 6 and 12 weeks. Alternatively, an ultrasound with potential biopsy may be recommended. If a nodule is visible by sonography as a distinct hypoechoic nodule, this increases the likelihood that it is HCC. Ultrasound may then be used to guide biopsy, if its location renders it accessible. It must be recognized, however, that guided biopsy may be false negative due either to sampling error or to occasional similarity between well-differentiated HCC and benign liver tissue. Therefore, negative results of a biopsy of indeterminate nodule should still trigger short-term imaging follow-up.

4.3. Probable HCC

These will be distinct nodules which are visible on more than one pulse sequence. Their distinction vs. the next category of risk will depend largely on the expertise and experience of the interpreting radiologists, as well as the quality of the MRI examination.

4.4. HCC

For these lesions, the characteristics of HCC are sufficiently clear that there is no reasonable doubt as to the diagnosis. It is becoming standard practice that a confident diagnosis from a reliable radiologist can be used to direct management decisions regarding HCC, in the absence of tissue diagnosis. In some instances, biopsy or documented rising α-fetal protein levels might be insisted upon, such as to list for transplantation, if the nodule is less than 2 cm diameter.

5. CONCLUDING STATEMENTS

Hopefully, the above discussions will help to improve communications between the various physicians involved in managing patients with HCC with regard to their diagnosis by MRI. As official criteria for assigning priority for liver transplant evolve, standards for reporting measurements of size and number may change. Regardless, it is important that all those involved in interpreting MR images and generating their reports are fully cognizant of the affects of these reports on patients' categories for prioritization.

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