

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Imaging Techniques for Hepatocellular Carcinoma



Claude Sirlin, MD
Professor of Radiology
University of California, San Diego
San Diego, California

H&O Is there a standardized protocol for the use of ultrasound in the surveillance of hepatocellular carcinoma?

CS Almost every major international society that has developed guidelines for the management of hepatocellular carcinoma (HCC) has advocated the use of ultrasound for surveillance. However, to my knowledge, no society has actually provided guidance on how the ultrasound surveillance protocol should be performed, interpreted, or reported. Therefore, ultrasound use is highly variable in HCC.

For example, from a technical standpoint, ultrasound surveillance could be anything from a cursory sweep of the liver with an ultrasound probe to a meticulous interrogation in both the transverse and sagittal planes. In addition to how meticulously the liver is searched, surveillance technique may vary in other ways. Depending on the operator and institution, the technique may or may not include looking at the portal veins and hepatic veins; looking at blood flow in the portal veins, hepatic veins, and hepatic artery; measuring the liver and vessels; looking for ascites outside of the liver; and evaluating the size of the spleen to search for evidence of portal hypertension.

The variability in ultrasound technique can be explained in part by the fact that surveillance may be performed by different types of operators. In some parts of the world, particularly in the United States, sonographers perform the ultrasound surveillance examinations. In other parts of the world, the ultrasounds may be performed by clinicians such as hepatologists or gastroenterologists. My opinion is that it does not necessarily

matter who performs the procedure as long as the individual is highly trained in the performance of ultrasound in patients with cirrhosis who are at risk for HCC and as long as the individual devotes attention to detail and performs a comprehensive examination.

Not only is there little or no standardization in surveillance ultrasound technique, but there is little or no standardization in terminology, interpretation, and reporting. As a result, interpretations may be unclear or ambiguous, and they may omit important information. These limitations can interfere with optimal management.

H&O What is the Liver Imaging Reporting and Data System, and what is its goal?

CS The variability associated with ultrasound also applies to computed tomography (CT) and magnetic resonance imaging (MRI). Similar to what was just described with ultrasound surveillance, there has been little if any standardization in CT or MRI of the liver in terms of technique, terminology, interpretation, and reporting. Therefore, the Liver Imaging Reporting and Data System (LI-RADS) has been established as an attempt to standardize these components of imaging. The ultimate goal is to promote better-quality examinations, more consistent interpretation, and clearer communication with patients and doctors so that both groups can have a better understanding of the disease and of the radiologist's thinking in order to formulate a better management plan.

LI-RADS, which originally focused only on CT and MRI with extracellular (conventional) contrast agents, was initially released in 2011 and then updated in 2013 and

2014. The 2014 update added MRI with hepatobiliary agents. Going forward, major updates will be released every 3 years. An ultrasound surveillance group was recently formed to standardize the technique, interpretation, and reporting of surveillance ultrasound, and a working group has also been formed to do the same for contrast-enhanced ultrasound. We are planning to introduce ultrasound and contrast-enhanced ultrasound components to LI-RADS by the end of 2015, prior to the next major LI-RADS update, which is scheduled for 2017.

H&O When should gadoxetate disodium be used for imaging of the liver?

CS This is a very complicated and interesting question. LI-RADS does not currently take a stand on whether gadoxetate disodium (Eovist, Bayer HealthCare) should be used. What LI-RADS has done is propose standardized technique, terminology, and interpretation for those radiologists and centers that use the agent. In addition, LI-RADS is planning to provide an interim update before the official update in 2017 on the pluses and minuses of this agent, which will hopefully allow radiologists to make informed decisions. We do not yet have enough scientific evidence to suggest whether or when gadoxetate disodium should be used, and we will not be in a position to do so until more scientific data become available. At that time, LI-RADS will be updated to incorporate these new data to inform radiologists, who, in partnership with hepatologists and surgeons, will decide which agent(s) to use.

H&O What are the advantages of this agent?

CS The main advantage of gadoxetate disodium is that it allows for the detection of neoplastic nodules, including high-grade dysplastic nodules, and early HCC based on underexpression of organic anion transporting polypeptides (OATPs) prior to hypervascularization.

Historically, HCC was detected by the elevation of blood flow, which occurs gradually as nodules progress from being benign to being frank malignancies in patients with cirrhosis and as the nodules become hypervascular in the arterial phase. The problem with this method is that cancer is present prior to the elevation of blood flow. With gadoxetate disodium, the expression of OATP can instead be used to detect cancers and precancerous nodules before they become hypervascular. As nodules become malignant, OATP expression decreases, which causes the nodules to appear hypointense (dark) relative to the liver and makes them identifiable as “defects” against the bright liver background. Importantly, the decrease in OATP expression tends to occur before the elevation of blood flow, so cancers can be detected earlier in their development. It is

particularly important to detect HCC earlier rather than later because by the time HCC is hypervascular it has usually acquired the ability to metastasize, which decreases the likelihood of a successful treatment.

Another advantage of gadoxetate disodium is that it sometimes allows us to detect HCCs with striking conspicuity even when HCCs may be missed with conventional contrast agents. The reason is that not all HCCs are hypervascular in the arterial phase, and some are only weakly hypervascular; without easily visible arterial enhancement, HCCs may be mistaken for nonmalignant nodules or may be missed altogether when using conventional agents. Using gadoxetate disodium, however, they may be detectable owing to OATP underexpression.

A third advantage is that in patients with cirrhosis, the liver is full of arterial portal shunts, which are microscopic connections between arteries and portal veins. These connections can look like small hyperenhancing nodules or cancers on MRI upon administration of a contrast agent, but they are not. With a conventional contrast agent, it can be very difficult to differentiate a small cancer from a small arterial portal shunt. However, by looking at the hepatobiliary phase of gadoxetate disodium, it is possible to differentiate true cancers from these vascular pseudolesions: true cancers appear as discrete dark nodules, whereas pseudolesions are not visible.

H&O What are the disadvantages of gadoxetate disodium?

CS One disadvantage is that gadoxetate disodium is administered only in small doses, so the timing of the arterial phase can be challenging, which can make the degree of enhancement more modest than with other agents. Therefore, hyperenhancement in the arterial phase may be more difficult to recognize.

In addition, gadoxetate disodium can be associated with transient dyspnea. Approximately one-fifth of patients who receive the agent experience a sensation of shortness of breath and cannot hold their breath well for 15 to 25 seconds when the arterial phase is acquired. These patients start breathing during the imaging, causing the images to look artifacted and potentially obscuring true lesions in the arterial phase.

A third disadvantage is that some major features can be more difficult to detect with this agent. According to LI-RADS, the diagnosis of HCC typically requires the presence of a capsule and/or washout. Gadoxetate disodium can make it more difficult to detect the capsule because the agent causes the surrounding liver to enhance markedly, which can obscure the enhancement of the tumor capsule and, thus, make it harder to establish the diagnosis of HCC. Gadoxetate disodium can also make it more difficult to characterize the presence of washout, which is another feature of HCC.

The last disadvantage of gadoxetate disodium is that it often does not work well in patients with very severe cirrhosis. The agent normally gets taken up by functioning liver cells. This is what causes the liver to appear bright and the HCCs to stand out as dark “defects.” However, if the liver is not functioning well, then the liver cells do not take up the gadoxetate disodium, the liver does not become as bright, and HCCs do not stand out as defects. In other words, the agent becomes ineffective.

H&O How and when should diffusion-weighted imaging be used in patients with HCC?

CS The quality of diffusion-weighted imaging is inconsistent in the liver for a variety of reasons. One reason is that there are often artifacts in the left lobe of the liver, making visualization of the left lobe and any nodules within it very difficult. There can also sometimes be difficulty visualizing the dome of the liver and any nodules in that location. Another challenge is spatial distortion; even if nodules are detected, it may be difficult to match their exact location on other sequences, which complicates our ability to interpret them. Therefore, there is currently not enough scientific evidence to require that diffusion-weighted imaging be used for HCC diagnosis.

Nevertheless, diffusion-weighted imaging is performed at many institutions because it can sometimes be helpful. When it works well, it can allow for the detection of small HCCs that might otherwise be missed. However, because the technical quality of diffusion-weighted imaging is inconsistent, LI-RADS does not require that institutions perform this modality. Instead, LI-RADS suggests that institutions use diffusion-weighted imaging only if they have the capability.

H&O How and when should CT scanning be used for HCC instead of MRI?

CS There is currently no high-level evidence to support the use of one modality over the other. Therefore, institutions should rely on whichever modality they feel they perform better. If an institution feels strongly that it performs CT better than MRI, then that institution probably should use CT. If another institution feels more comfortable with MRI, then that institution should use MRI. Many academic centers prefer MRI, but that does not necessarily mean that all centers should use MRI.

Nevertheless, I believe that even in institutions that prefer CT, MRI could be valuable as a problem-solving tool. If indeterminate lesions are detected on CT, MRI might be helpful in further characterization.

H&O What are the next steps in research?

CS Studies are needed to either validate or refute different portions of LI-RADS so that we can improve and simplify the algorithm. For example, we need to better understand whether we should have the same criteria for CT, MRI with gadoxetate disodium, and MRI with extracellular agents. In addition, we need to determine whether ancillary features, such as diffusion-weighted imaging properties and T2 properties, can be integrated into the diagnosis of HCC. Right now, the diagnosis of HCC is based on enhancement in arterial phase, washout appearance, and capsule appearance.

Likewise, studies should be conducted on integrating imaging features across modalities. For example, patients often undergo a combination of imaging modalities, such as MRI and CT, MRI with an extracellular agent, MRI with gadoxetate disodium, or contrast-enhanced ultrasound and CT. How can we obtain an integrated interpretation from multiple modalities?

Another area of research involves multifocal HCC. Right now, LI-RADS, as well as all other systems, has been designed to categorize a single nodule or observation. However, how does the presence of multiple nodules or observations change the interpretation of the overall examination? Intuitively, one would think that if a patient has a nodule that is “LI-RADS 4, probably HCC,” the patient has a certain probability of cancer. However, what if a patient has 5 or 6 observations, each of which individually is LI-RADS 4 (ie, probably HCC)? Intuitively, one would think that these findings would greatly increase the likelihood of having multifocal HCC. However, this is not yet definitively known nor integrated into any clinical practice guidelines.

Lastly, longitudinal studies are needed to determine whether the LI-RADS categories can predict outcomes and whether the use of LI-RADS can improve patient management and clinical decision-making. Ultimately, we need to determine whether the use of LI-RADS can improve patient outcomes.

Dr Sirlin has received research grants from GE Healthcare, Siemens, and Guerbet.

Suggested Reading

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A copy of this interview is appearing in the June 2015 issue of *Gastroenterology & Hepatology*.