Hepatocellular carcinoma (HCC) is one of the world’s most common cancers. It is closely associated with cirrhosis, especially that due to viral hepatitis. The incidences of viral hepatitis and HCC are rising steadily in the United States. Cirrhosis is estimated to develop in 20% of patients after 10 years of chronic HCV infection. Hepatocellular carcinoma occurs at a rate of 1% to 4% per year after cirrhosis is established. According to a consensus report by the National Institutes of Health, the annual probabilities of developing liver cancer are 0.5% among those with chronic HBV and 2.4% after the onset of cirrhosis. Although the precise mechanism of hepatocarcinogenesis is unknown, some pathogenetic factors have been defined. Hepatocellular carcinoma almost always occurs in the setting of chronic hepatocyte injury and inflammation. The subsequent regenerative response and fibrosis lead to cirrhosis. This, in turn, may enhance genetic mutations that lead to the eventual development of carcinoma. Both HBV and HCV may be involved in multiple steps along this disease pathway. Through chronic infection, the viral genome may become incorporated into the hepatocyte DNA and may produce genetic instability and mutations. Patients with symptomatic HCC usually present with abdominal pain, weight loss, jaundice, and abdominal distention resulting from uncontrollable ascites or tumor mass.

In the United States, both chronic viral hepatitis and HCC are occurring with increasing frequency. Currently, there are approximately 3.9 million people infected with HCV and between 1 and 1.25 million infected with HBV in the United States. Cirrhosis is estimated to develop in 20% of patients after 10 years of chronic HCV infection. Hepatocellular carcinoma occurs at a rate of 1% to 4% per year after cirrhosis is established. According to a consensus report by the National Institutes of Health, the annual probabilities of developing liver cancer are 0.5% among those with chronic HBV and 2.4% after the onset of cirrhosis.

Hepatocellular carcinoma (HCC) is one of the world’s most common cancers. The global distribution of HCC correlates with the geographic prevalence of chronic viral hepatitis and cirrhosis. Regions with a high incidence of HCC (> 30 cases per 100,000 population) include sub-Saharan Africa, Southeast Asia, and Southern China; North America and Western Europe have a low incidence (< 2 cases per 100,000). Individuals with persistent hepatitis B virus (HBV) or hepatitis C virus (HCV) infection have 100 times the relative risk of developing HCC as do uninfected persons.

In 1995, the International Working Party developed a nomenclature system for hepatocellular nodules. The lesions were categorized according to the presence of dysplasia vs regeneration and according to the anatomy of the surrounding liver parenchyma. Regenerative nodules are the result of localized proliferation of hepatocytes and their supporting stroma. The regenerative nodule represents a fundamental response to decreased functional liver cell mass and is presumably the result of increased levels of local growth factors. When regenerative nodules are distinctly larger than most cirrhotic nodules in the same liver (generally at least 5 mm or greater), they may be called large regenerating nodules or macroregenerative nodules. The cells in a regenerative nodule are histologically the same as in the adjacent parenchyma. A dysplastic nodule is a region of hepatocytes with dysplasia but without definite pathologic criteria of malignancy. These nodules are usually, but not always, found in cirrhotic livers. Dysplastic nodules may occur in any size. As the size of the lesions increases, the prevalence of high-grade or malignant lesions also increases.
Differentiating Nodular Lesions From HCC

Regenerative nodules, dysplastic nodules, and HCC represent a continuum of the same disease process. Thus, differentiating a large regenerative nodule from a low-grade dysplastic nodule or a high-grade dysplastic nodule from HCC is often impossible. Dysplastic nodules should be diagnosed if there are features suggestive of a neoplastic process. High-grade dysplastic nodules should be diagnosed if the neoplastic features are very similar to those seen in malignancy. The criteria to distinguish high-grade dysplastic nodules from HCC are arbitrary and depend on how much the lesion resembles HCC. The most accurate way to distinguish a regenerative nodule from a dysplastic nodule and HCC may be through the use of molecular genetic techniques. Foci of carcinoma are present in approximately 30% of otherwise benign dysplastic nodules on serial sectioning.[10] Thus, a diagnosis of HCC cannot be excluded in any dysplastic nodule that is sampled only with a needle biopsy.

Screening for HCC

To screen for a disease, asymptomatic people generally undergo a test or tests in the hope of detecting the disease early in its course. For a screening program to be effective, it must meet several criteria:

1. The disease must have a high prevalence and result in significant morbidity.
2. The natural history of the disease must allow for effective treatment when it is diagnosed at an asymptomatic stage.
3. The test must have acceptable sensitivity and specificity.[11]

Since the predictive value of a test depends on the prevalence of the disease in question, an effective screening program for HCC must focus on a high-risk population. Mass population screening programs for HCC are feasible in Asian countries where there is a high incidence of the disease. In the West, however, where the prevalence of HCC is low, only patients with chronic viral hepatitis and compensated cirrhosis require screening.

Most HCC screening protocols use ultrasound and serum alpha-fetoprotein (AFP), although the use of AFP as a screening test is complicated by frequent false-negative and false-positive results. Kang et al reported a sensitivity of 68% and specificity of 20% using AFP to diagnose early (less than 3 cm) HCC.[12] In another study from China, serum AFP levels were elevated only in 60% to 70% of patients with small HCC lesions, and fewer than 20% of the elevated levels of AFP were due to HCC. Acute-on-chronic hepatitis was the most common cause of elevated AFP.[13] There have been several reports of sonographic screening for HCC in high-risk patients.[14-16] Although ultrasound is probably a more sensitive screening tool than AFP, it also produces a high number of false-positive findings in a multinodular, cirrhotic liver.[17] Ultrasound is an operator dependent modality, and, as a result, examination quality may vary widely. Okuda et al reported that only 60% of nodules identified by ultrasound in a cirrhotic liver were biopsy-positive HCC.[17] With recent advances in hepatic imaging techniques, small nodular lesions of undetermined malignant potential are being detected with increasing frequency in cirrhotic livers.[18] These lesions are also increasingly noted on liver explant pathology.[19]

In the past, small nodular lesions of undetermined malignant potential have been classified as adenomatous hyperplasia, macroregenerative nodules, nodular hyperplasia, dysplastic nodules, adenomatous hyperplastic nodules, atypical adenomatous hyperplasia, or adenomatous hyperplasia with malignant foci. These lesions may vary histologically from benign, large regenerating nodules to equivocally malignant nodules to nodules containing obvious malignant foci.[20] Distinguishing benign from malignant or premalignant disease is clinically important because early surgical intervention provides the only opportunity for cure.

Hepatic MRI

Radiologic evaluation of HCC can be complex. Ultrasound and computed tomography (CT) are valuable screening tools. However, lesions that cannot be fully characterized by these modalities should be evaluated further with magnetic resonance imaging (MRI). Recent advances in MRI technology, including faster protocols, breath-hold imaging, and the use of contrast agents, such as gadolinium chelates, ferumoxides particles (Feridex I.V.), and mangafodipir trisodium injection
Gadolinium is the most widely used hepatic contrast agent. It is a nonspecific extracellular space agent that distributes in a pattern similar to water-soluble iodinated contrast agents.

Newer tissue-specific agents include ferumoxides particles and mangafodipir trisodium injection. Iron oxide particles are taken up by cells of the reticuloendothelial system (Kupffer cells). Hepatocellular carcinoma and metastatic lesions lack these cells and therefore do not take up iron oxide particles, thus producing a negative contrast. Iron oxide is especially useful in identifying small lesions that may be overlooked on gadolinium-enhanced MRI (Figure 1).

Mangafodipir trisodium injection is avidly taken up by normal hepatocytes. Most HCCs will take up manganese, and a well-differentiated HCC may show greater enhancement than surrounding liver, reflecting persistent hepatocellular dysfunction with decreased biliary clearance. Thus, manganese has limited usefulness in the evaluation of a nodule suspicious for HCC.

**Imaging Nodular Lesions in a Cirrhotic Liver**

Hepatocellular carcinoma generally arises in the cirrhotic liver, and cirrhosis causes distortion of the hepatic parenchyma. Changes in the parenchyma range from regenerative nodules to dysplastic nodules to HCC.

Regenerative nodules can be difficult to image with CT or ultrasound. On MRI, regenerative nodules are also often difficult to distinguish but may appear as isointense nodules on T1-weighted images and as low-signal intensity nodules on T2-weighted and gradient-echo images. Dysplastic nodules do not image well with ultrasound or CT. On MRI, these nodules may produce high-signal intensity on T1-weighted images and low-signal intensity on T2-weighted images, and they may show homogeneous hyperintense enhancement after administration of gadolinium chelates, simulating HCC.

The use of MRI to identify and characterize regenerative and dysplastic nodules is still nonspecific and often unrewarding, however. Typically, lesions are not well demonstrated in the cirrhotic liver until they have evolved to actual HCCs.

Hepatocellular carcinoma has been extensively studied with MRI. It may appear as hyperintense, isointense, or hypointense lesions on T1-weighted images. Generally, HCCs are high-signal intensity lesions on T2-weighted images.

Small lesions may be seen only with contrast-enhanced images and appear as hyperintense, enhancing lesions on the arterial phase. Dynamic contrast-enhanced imaging usually displays HCCs as hypervascular and hyperintense (Figure 2A). Because of variable cardiac output and the vascular flow anomalies associated with cirrhosis, a dynamic MRI protocol with a single fixed-time delay for imaging of the arterial phase is often suboptimal. Multiple successive images of the entire liver from the early arterial phase may allow for the detection of very small HCC lesions. "Wash-out" of the lesion on portal-venous phase and delayed images occurs as the contrast medium rapidly leaves the lesion and the degree of enhancement dissipates (Figure 2B).

Large lesions may enhance heterogeneously after administration of a gadolinium contrast medium. Often, larger lesions will exhibit visible calcifications or a central scar. Focal macroscopic adipose tissue within a tumor or the coexistence of a liver mass and portal-vein thrombosis is highly suggestive of HCC.

Fibrolamellar carcinoma is an uncommon variant of HCC. It occurs in younger patients and is less commonly associated with chronic liver disease.

Fibrolamellar tumors are usually large and solitary and have low-signal intensity on T1-weighted images and heterogeneous or bright-signal intensity on T2-weighted images. The characteristic central scar of fibrolamellar HCC may produce low-signal intensity on T2-weighted images but does not enhance following administration of a contrast agent. The remainder of the mass enhances heterogeneously and robustly on images taken immediately after contrast administration.

**Imaging Protocol at Baylor**

The imaging protocol for the diagnosis of HCC in a cirrhotic liver at Baylor University Medical Center includes the following imaging sequences:

1. Coronal and axial single-shot fast spin echo breath-hold T2-weighted imaging. This sequence is used to identify lesions other than HCC, including hemangiomas or benign cysts that will appear as very bright signal intensities. Hepatocellular carcinoma will produce only moderately bright signal intensity.
2. Gradient breath-hold T1-weighted in-phase and out-of-phase imaging—This is used to identify focal fat (steatosis) within the lesions. Hepatocellular carcinoma and RN can have focal areas of steatosis. The focal fatty areas lose signal intensity on out-of-phase imaging compared to in-phase imaging.

3. Dynamic post-gadolinium gradient breath-hold T1-weighted images obtained (1) during injection of gadolinium, (2) immediately following injection, (3) at 3 minutes, and (4) at 10 minutes following injection—These sequences identify arterially enhancing lesions and subsequent rapid wash-out of gadolinium usually seen with HCC. Delayed images are obtained to evaluate for late enhancement, such as is seen with cholangiocarcinoma.

Pretransplant Screening at Baylor

The pretransplant evaluations of 269 consecutive orthotopic livers at Baylor University Medical Center were reviewed to determine the best screening modality for detecting occult HCC in a multinodular, cirrhotic liver. The evaluation included focused hepatic ultrasound (N = 261), gadolinium-enhanced MRI (N = 240), and serum AFP (N = 252).

The primary pretransplant diagnoses are listed in Table 2. Patients with chronic active viral hepatitis and alcoholic cirrhosis comprised 57% of the group. Serologic evidence of viral hepatitis was present in 148 patients (55%). All explanted livers were subjected to a full pathologic evaluation. Hepatocellular carcinoma was found in 21 explanted livers (8%). In the cohort of 156 patients with chronic active viral hepatitis or alcoholic cirrhosis, 19 (12%) had HCC in the explanted liver.

All patients were noted to have a multinodular, cirrhotic liver by both ultrasound and MRI. A dominant nodule, distinct from the multinodular background, was identified in 37 patients by MRI vs 33 patients by ultrasound. Magnetic resonance imaging was more sensitive than ultrasound (68% vs 43%), although ultrasound and MRI were both 99% specific for diagnosing a nodule as HCC. The positive predictive values of MRI and ultrasound were 87% and 97%, respectively, and the negative predictive values of the two tests were 90% and 95%, respectively. An elevated AFP (> 20 ng/dL) was noted in 47% of patients with HCC and in only 10% of patients without HCC.

Conclusions

The diagnosis of HCC in a multinodular, cirrhotic liver is a difficult clinical problem. With the recent development of improved resectional and ablative therapies, cirrhotic patients are now eligible for the treatment of HCC. The potential for cure of HCC depends on early detection.

Screening of high-risk patient populations will be necessary to achieve early diagnosis. Because of the high sensitivity and lack of operator dependence of MRI, it appears to be a more useful imaging modality than ultrasound for detecting HCC in a cirrhotic liver. These data suggest that the ideal screening for HCC in the cirrhotic liver should include monitoring serum AFP and imaging with gadolinium-enhanced MRI at regular intervals.

References:
1997.


