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Review Article

THE ROLE OF IMAGING IN DIAGNOSIS OF HEPATOCELLULAR CARCINOMA(HCC)

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the world's most common cancersand its incidence is expected to rise rapidly over the next decade due to the , association with chronic liver disease, particularly HBV and HCV. Many patients known to have chronic liver disease are now being screened for the development of HCC by serial ultrasound scans of the liver or serum measurements of alpha-fetoprotein (AFP). Patients often present in middle age, either because of the symptoms of chronic liver disease (malaise, weakness, jaundice, ascites, variceal bleed, encephalopathy) or with the anorexia and weight loss of an advanced cancer. Diagnosis of HCC often requires more sophisticated imaging modalities such as ultrasound, CT scan and MRI, which have multiphasic contrast enhancement capabilities. Serum AFP used alone can be helpful if levels are markedly elevated, which occurs in fewer than half of cases at time of diagnosis. Confirmation by liver biopsy can be performed under circumstances when the diagnosis of HCC remains unclear.The surgical treatment options include resection of the tumour and liver transplantation. Which option is most appropriate for an individual patient depends on the stage of the underlying liver disease, the size and site of the tumour, the availability of organ transplantation and the management of the immunosuppressed patient.

Key Points: Ultrasound, CT scan ,MRI, Angiography.

INTRODUCTION

Hepatocellular carcinoma is one of the most common malignant tumors, particularly in Southeast Asia, subSaharan Africa, Japan, Greece, and Italy. HCC occurs predominantly in men, with a male/female ratio of approximately 5 :1.(1) Etiologic factors depend on the geographic distribution. Although alcoholic cirrhosis remains a common predisposing cause for hepatoma in the West, both hepatitis C and hepatitis B are now of worldwide signifcance. These viral infections also account for the high incidence of HCC in sub-Saharan Africa, Southeast Asia, China, Japan, and in the Mediterranean. Of growing importance in the Western world, fatty liver with the development of steatohepatitis is increasing in signifcance as an antecedent to the development of cirrhosis and HCC. Aflatoxins, toxic metabolites produced by fungi in certain foods, have also been implicated in the pathogenesis of hepatomas in developing countries.(2)

The **clinical presentation** of HCC is often delayed until the tumor reaches an advanced stage. Symptoms include RUQ pain, weight loss, and abdominal swelling when ascites is present.

Pathologically, HCC occurs in the following three forms:

Solitary tumor

Multiple nodules

Diffuse infltration

There is a propensity toward venous invasion. The portal vein is involved in 30% to 60% of cases and more often than the hepatic venous system.(3,4,5)

Utlrasound

The **sonographic appearance of** HCC is variable.

The masses may be hypoechoic, complex, or echogenic. Most small (<5 cm) HCCs are hypoechoic (Fig. 1, *A*), corresponding histologically to a solid tumor without necrosis.(6,7) A thin, peripheral hypoechoic halo, which corresponds to a fbrous capsule, is seen most often in small HCCs.(8)

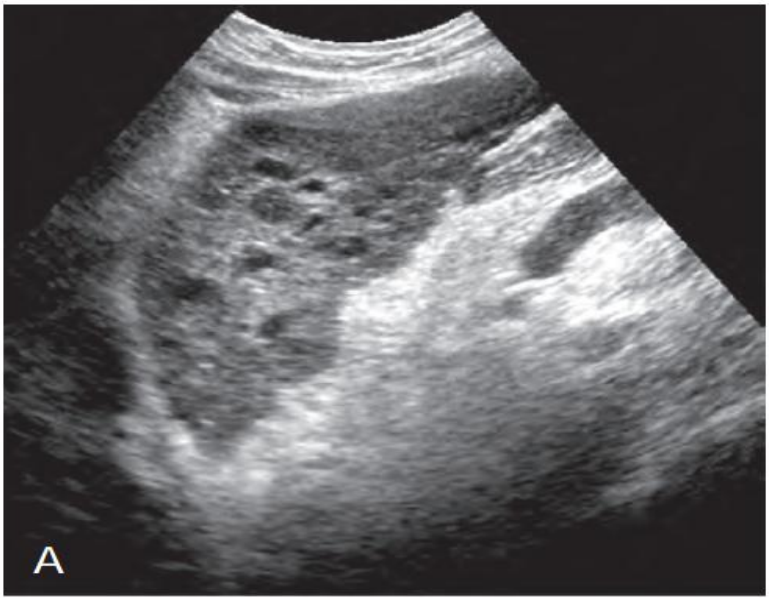

Figure 1: Hepatocellular carcinoma: A, Small, focal hypoechoic nodules.

With time and increasing size, the masses tend to become more complex and inhomogeneous as a result of necrosis and fbrosis (Fig. 2, *E*).

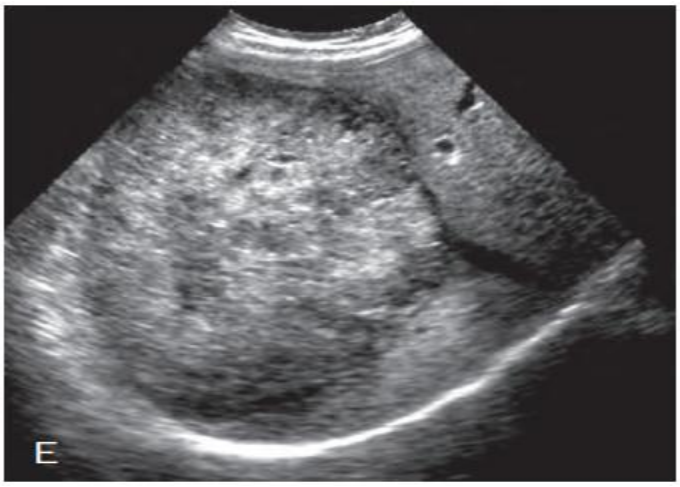

Figure 2: E, Large mixed-echogenic mass.

Calcifcation is uncommon but has been reported.190 Small tumors may appear diffusely hyperechoic, secondary to fatty metamorphosis or sinusoidal dilation (Fig. 3, *C*), making them indistinguishable from focal fatty infltration, cavernous hemangiomas, and lipomas.(6,7,10) Intratumoral fat also occurs in larger masses; because it tends to be focal, it is unlikely to cause confusion in diagnosis.

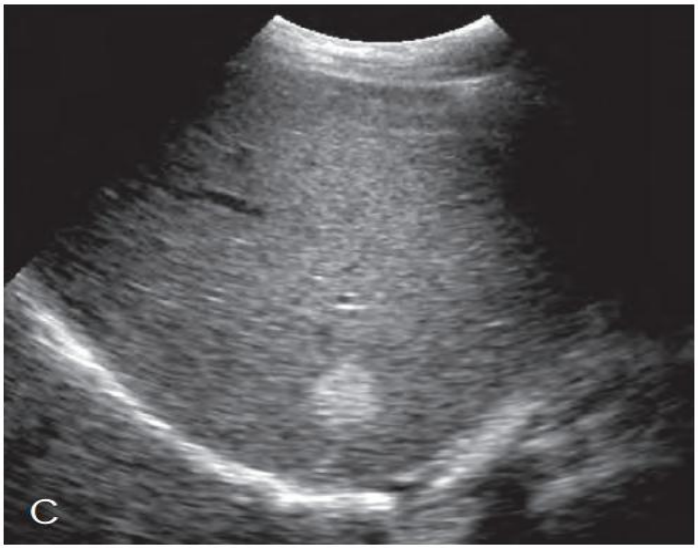

Figure 3: C, Focal echogenic nodule mimicking hemangioma

Patients with rare surface lesions may present with spontaneous rupture and hemoperitoneum (Fig. 4, *I*).

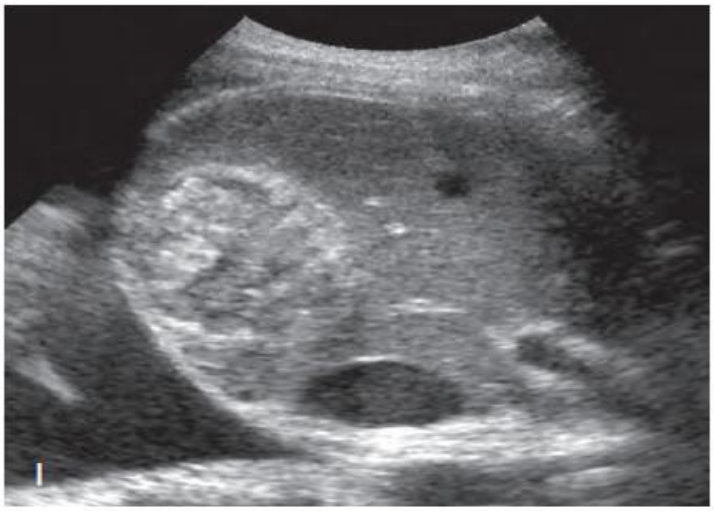

Figure 4: I, Superfcial mass of mixed echogenicity in a young hepatitis B patient presenting with spontaneous liver rupture.

Studies evaluating focal liver lesions with duplex Doppler and CDFI suggest HCC has characteristic high-velocity signals.(11-13) Doppler sonography is excellent for detecting neovascularity within tumor thrombi within the portal veins, diagnostic of HCC even without demonstration of the parenchymal lesion (Fig. 5).

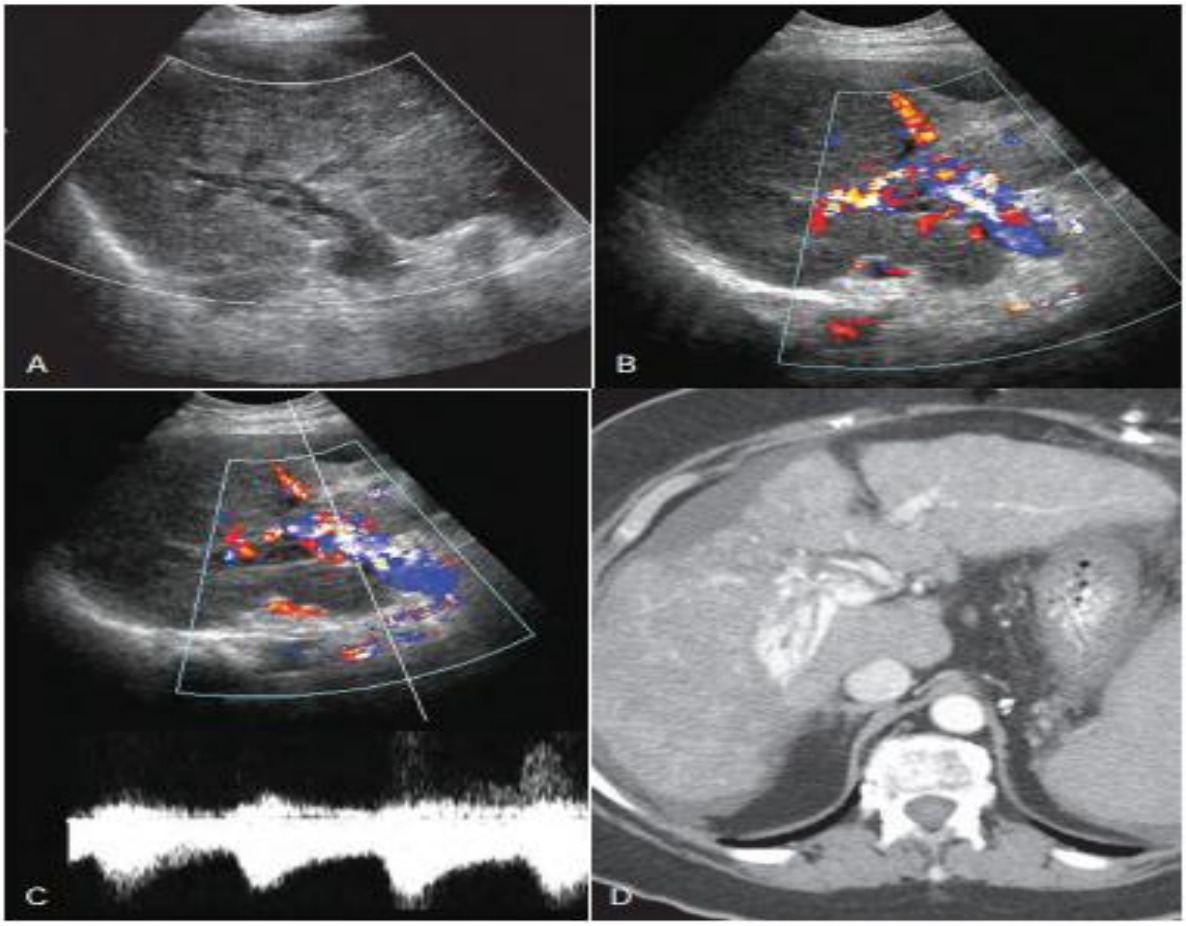

Figure 5: Malignant portal vein thrombus from hepatocellular carcinoma. A, Long-axis view of the portal vein

Shows extensive intraluminal soft tissue masses.**B,** Addition of color Doppler flow imaging shows a disorganized flow pattern with multiple flow velocities and color aliasing. **C,** Spectral waveform from within the lumen of the portal vein shows arterial waveforms suggesting neovascularity

Highly superior to conventional Doppler sonography for characterization of **HCC in the cirrhotic liver, microbubble CEUS** is much more sensitive for the detection of lesional vascularity (Table 1).

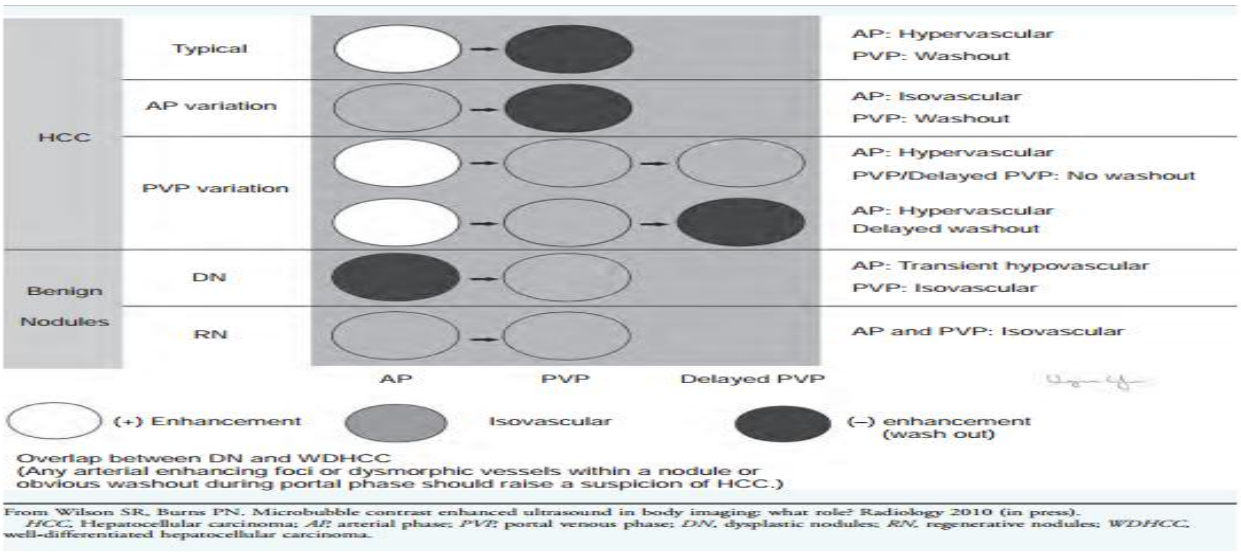

Table 1: Schematic Of Algorithm For Diagnosis Of Nodules In Cirrhotic Liver On Ceus

Lesions are hypervascular, often showing dysmorphic vessels (see Fig. 6, *B*) and frequently showing unenhanced regions representing either necrosis or scarring (14,15) (Fig. 7).

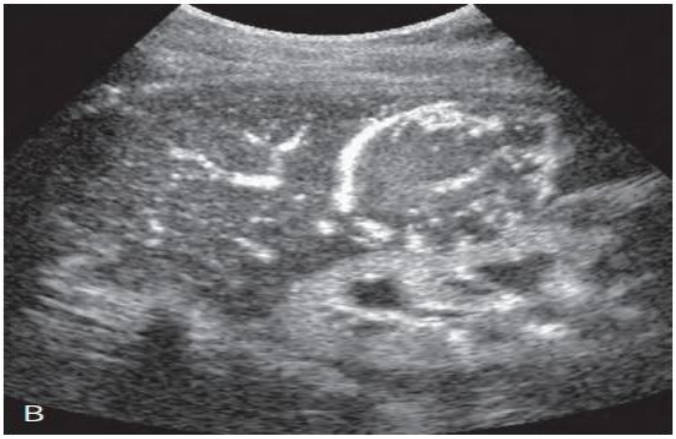

Figure 6: Hepatocellular carcinoma. **B,** Vessels in the anterior part of the lesion are tortuous and dysmorphic.

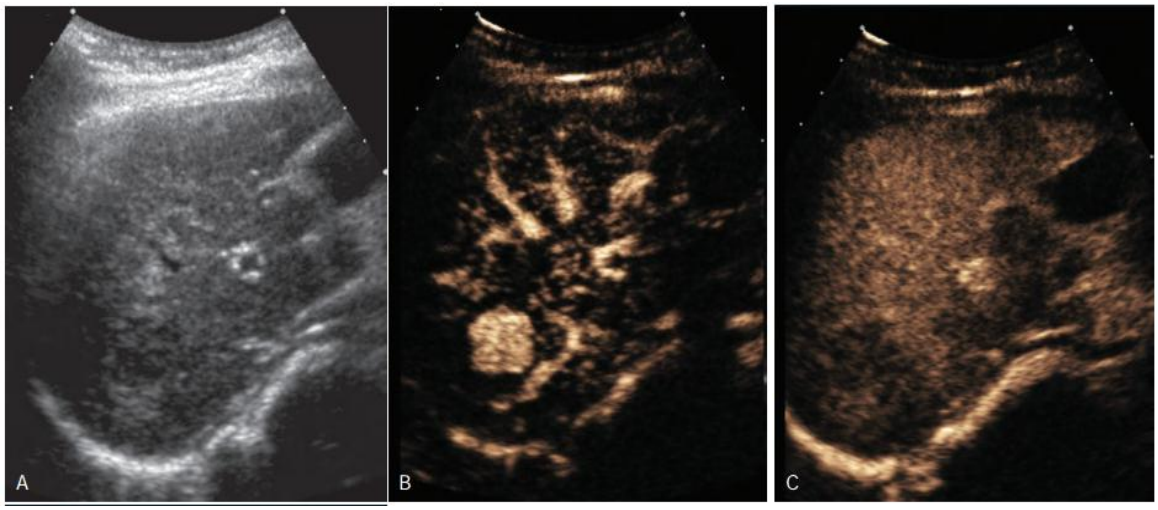

Figure 7: Classic hepatocellular carcinoma (HCC) detected on surveillance ultrasound.

A, Small hypoechoic mass in the right lobe of a small cirrhotic liver. **B**, Contrast-enhanced ultrasound (CEUS) image at the peak of arterial phase enhancement shows classic hypervascularity. **C**, CEUS image in the portal venous phase at 2 minutes. The lesion has washed out relative to the more enhanced liver. *(From Wilson SR, Burns PN. Microbubble enhanced ultrasound imaging: what role? Radiology 2010 [in press].)*

In the portal venous phase, lesions show washout, such that they are less enhanced than the adjacent liver (see Fig. 8 *F*). Variations to this classic pattern are now well described14 and include arterial phase hypovascularity and delayed or no washout in the portal venous phase (Fig. 9).

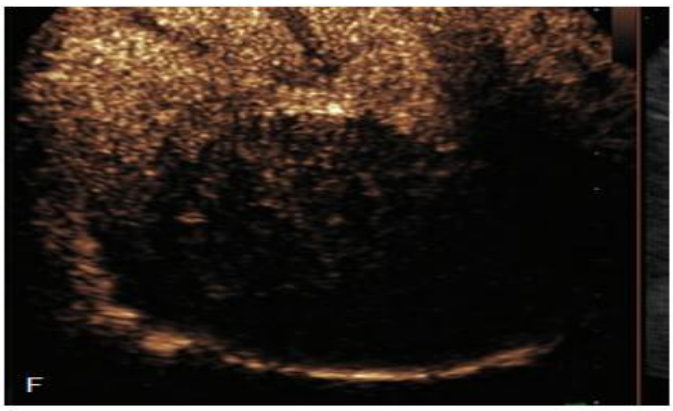

Figure 8: F, Portal venous phase image shows that the liver is enhanced. The lesion is less echogenic than the liver or has "washed out."

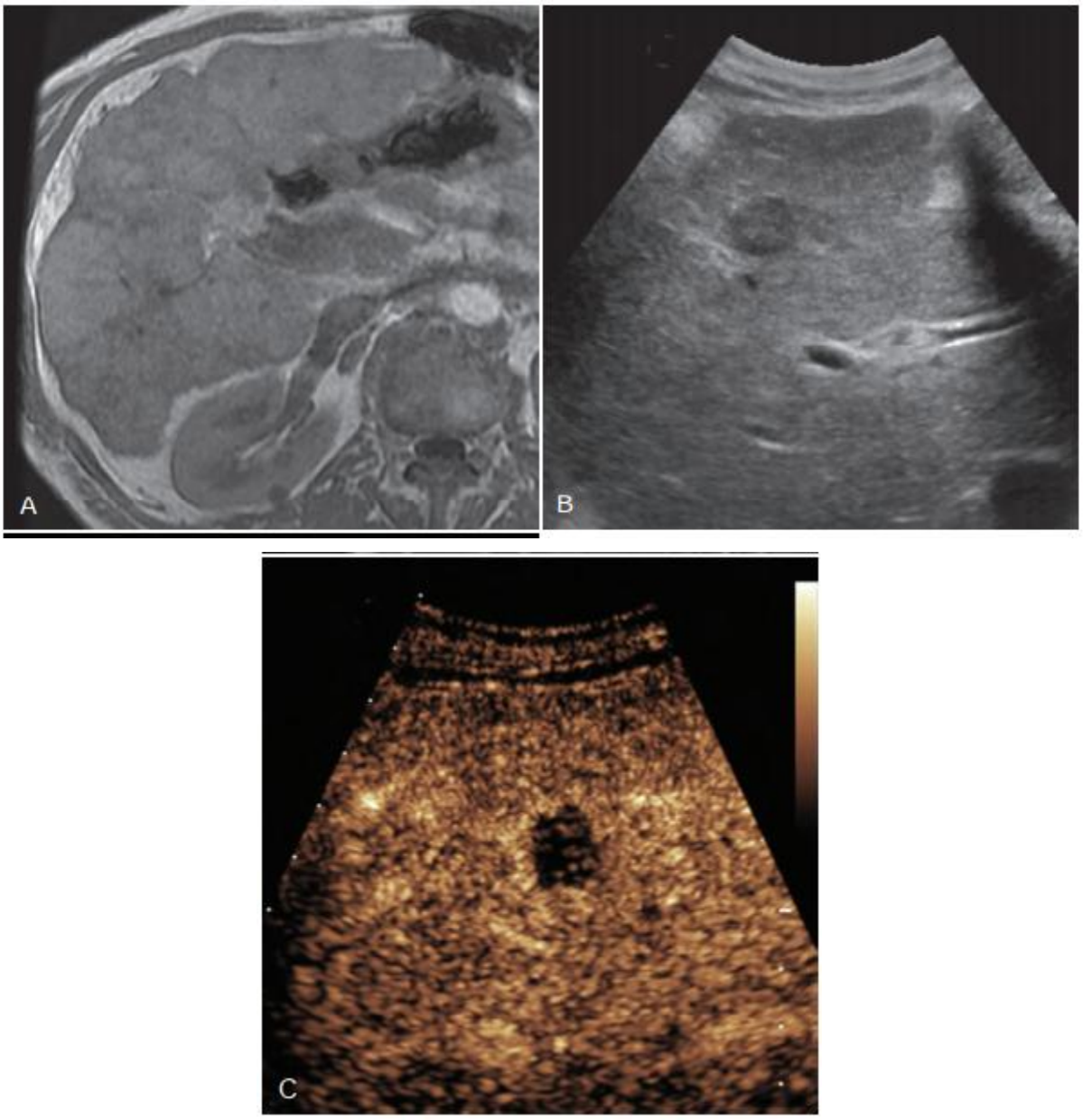

Figure 9: Multimodality approach to diagnosis of hepatocellular carcinoma.

Small HCC in 59-year-old man with ethanol and hepatitis C virus (HCV) cirrhosis. **A**, Good-quality MRI scan is negative, showing no mass on T2-weighted images and no hypervascularity on enhanced scan, the representative image shown here. **B**, Baseline sonogram shows a single hypoechoic nodule in the right lobe of the cirrhotic liver. **C**, CEUS arterial phase image shows clear hypovascularity of the mass. The mass quickly became isovascular and did not show washout. Familiarity with the variations of enhancement patterns of HCC on CEUS prompted request for biopsy, which showed a moderately differentiated HCC. *(From Wilson SR, Burns PN. Microbubble enhanced ultrasound imaging: what role? Radiology 2010 [in press].)*

Regenerative **nodules,** by comparison, show similar arterial phase and portal venous phase vascularity and enhancement to the remainder of the cirrhotic liver. **Dysplastic nodules** may show transient arterial phase hypovascularity followed by isovascularity. Identifcation of this feature prompts biopsy in our institution. Microbubble-enhanced sonography may contribute also to the detection of HCC. Sweeps of the liver in the arterial phase may detect hypervascular foci potentially representing HCC. Sweeps in the portal venous phase, by comparison, show HCC as hypoechoic or washout regions, again allowing for the detection of unsuspected lesions. The arterialized liver of cirrhosis, however, is problematic for several reasons. First, itshows dysmorphology of all liver vessels, in general, and the appreciation of focal increased vascularity in a small nodule is more diffcult. Portal venous phase imaging is also weakened when the liver receives a greater proportion of its blood supply from the hepatic artery. Therefore, washout of a specifc nodule may not be as evident as in a normal liver. This area remains of high interest to us, and ongoing investigations are evaluating chronically diseased livers. CT16 and MRI17 are frequently performed to screen for and evaluate HCC. The importance of CEUS is recognized by the American Association for the Study of Liver Diseases (AASLD) and has been included in the practice guideline for the management of small nodules detected in the surveillance for HCC.18

CT Scan (19-24):

Unenhanced CT may demonstrate focal or multifocal HCC as ill-defined low-attenuation lesions. Focal areas of internal calcification have been described in up to 7.5 per cent of lesions. The majority of HCCs are hypervascular and enhance during the arterial phase, with some lesions tending to merge with the background in the portal phase and others remaining of relative low attenuation. Some lesions show a ‘mosaic’ pattern of enhancement on CT with an enhancing grid-like pattern around central lower areas of attenuation. Arterial phase CT has proved more sensitive for the detection of HCC than older CT techniques, as some 10 per cent of lesions are only visible during the arterial phase (Fig. 10).

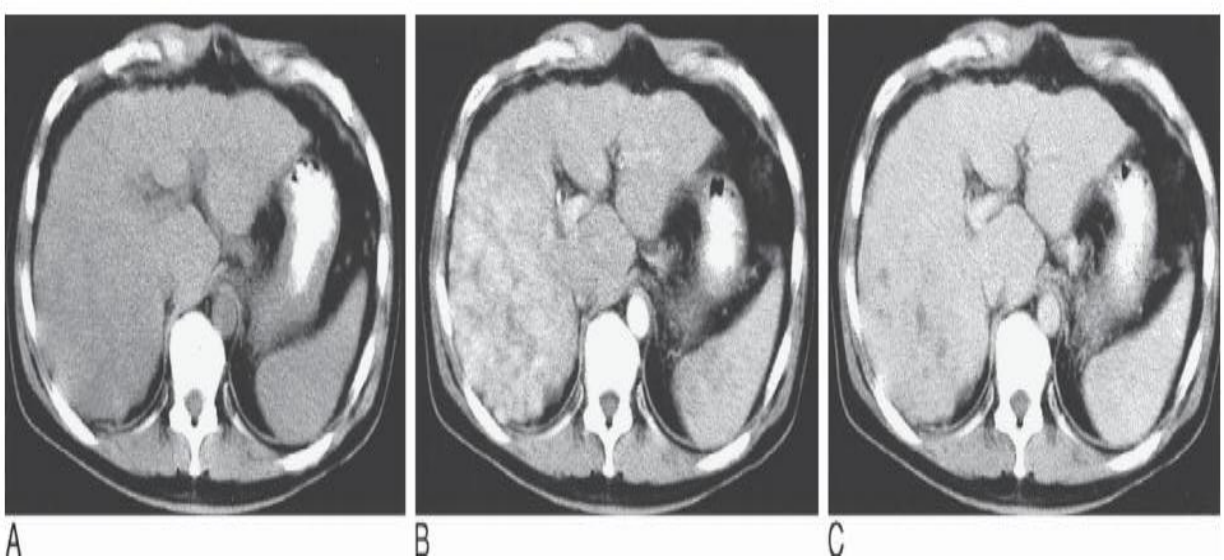

Figure 10: Multi-focal HCC.

A biphasic CT (unenhanced (A), arterial phase (B) portal phase (C)) examination demonstrates the multifocal and extensive nature of the tumour, which is only fully apparent during the transient enhancement of the arterial phase.

Arterial phase images may also allow the demonstration of arterial branches in tumour thrombus. The CT features of portal venous invasion by hepatocellular carcinoma include arterioportal fistulae, periportal streaks of high attenuation, and dilatation of the main portal vein or its major branches. Although portal venous invasion is thought to be a specific feature of hepatoma (Fig. 11), portal venous thrombosis can also be seen in patients with hepatic metastases, which cause portal venous compression. Arterial infusion of lipiodol followed 7–10 d later by CT examination is widely used in Asia for the detection of HCC but is not commonly used in other parts of the world, where arterial phase CT or MR has largely replaced it.

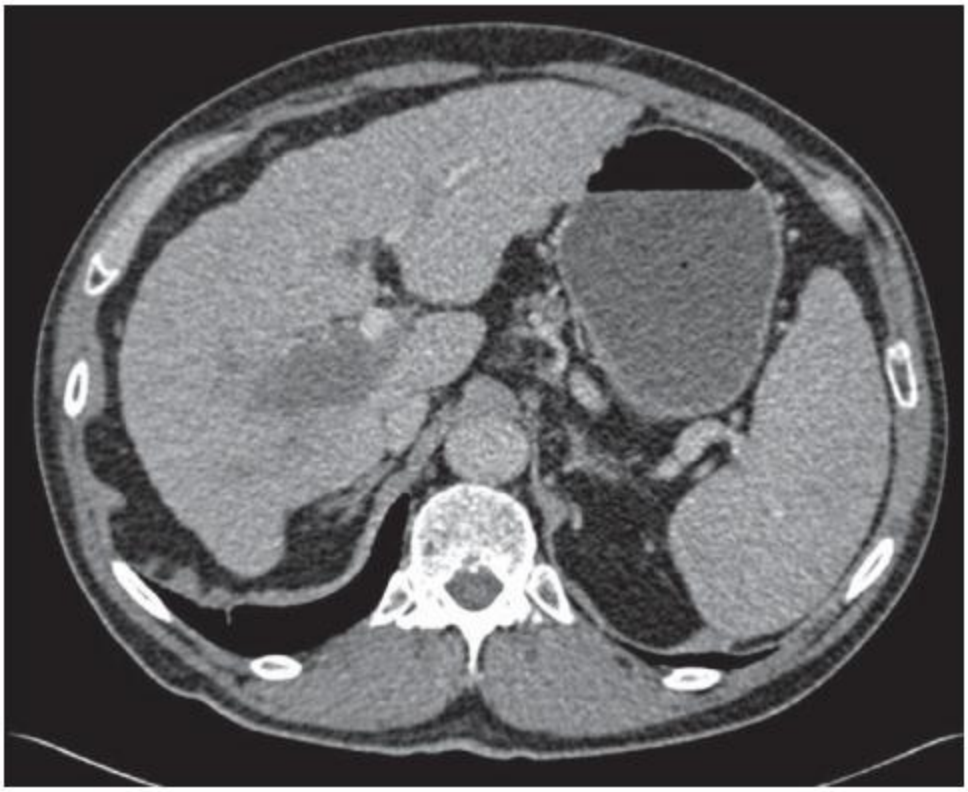

Figure 11: Portal venous invasion by hepatocellular carcinoma.

CT in the portal phase demonstrates an expanded low attenuation region in the location of the right portal vein. The expansion of the vein is suspicious of underlying tumor and was supported by arterial vascular signals in this lesion at US. Biopsy confirmed an invasive hepatocellular carcinoma.

MRI(25-26):

On MRI,hepatoma is typically of decreased signal on T1w and moderately increased signal on T2w often but not always with internal heterogeneity (Fig. 12).

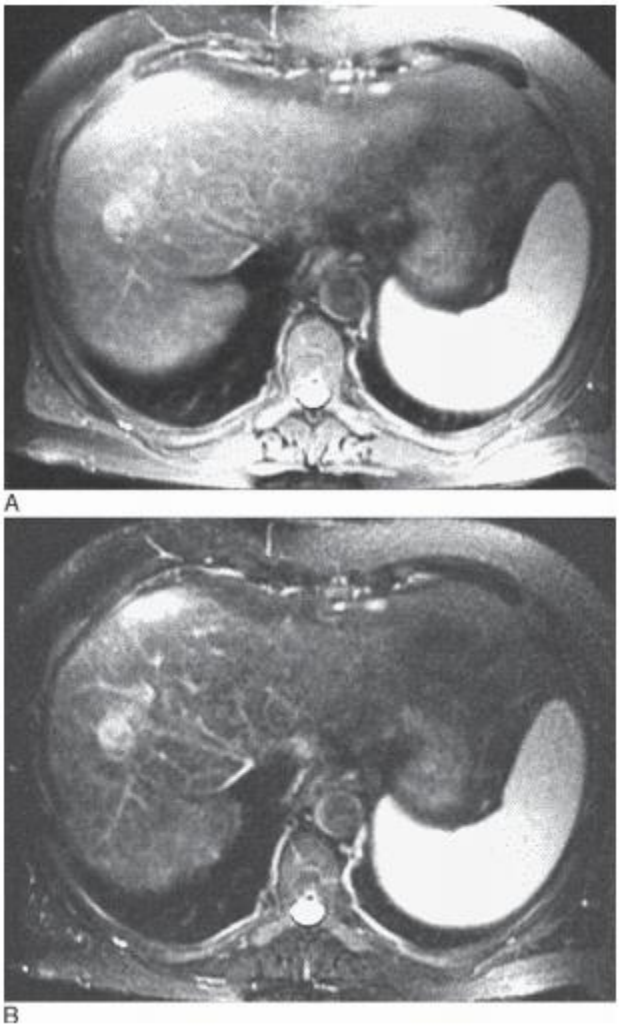

Figure 12: Hepatocellular carcinoma.

An irregular margin heterogeneous ('mosaic' pattern) lesion is present in the right lobe on T2w MRI. The lesion is of increased signal on T2w but similar to the spleen on both TE 60 ms (A) and TE 120 ms (B).

Some lesions are of increased signal on T1w probably due to fat or possibly glycogen accumulation rather than copper as previously thought (Fig.13).

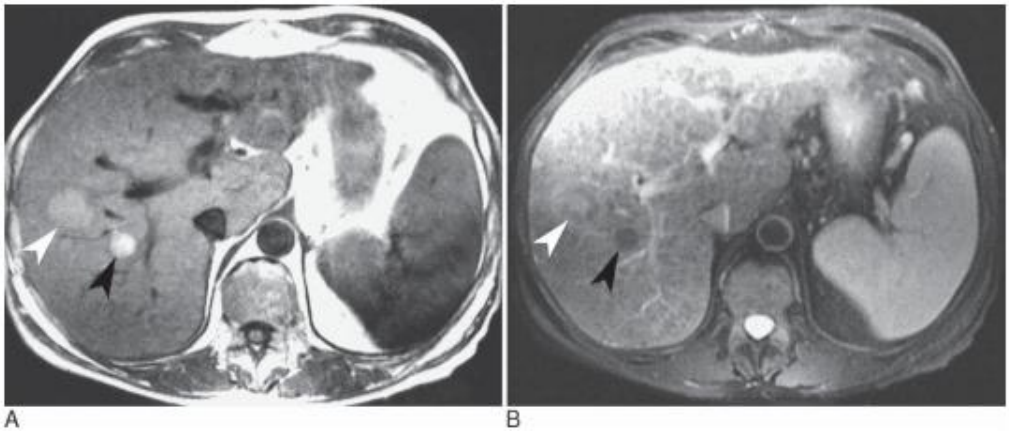

Figure 13: Hepatocellular carcinoma and regenerative nodule.

T1w MRI (A) and T2w MRI (B) demonstrating a hepatocellular carcinoma (white arrowhead) and an adjacent atypical regenerative nodule (black arrowhead). Although the majority of hepatomas have decreased signal intensity on T1w occasionally they have increased signal, thought to relate to fat or glycogen content. Note the heterogeneity in the hepatoma, particularly on T2w. The findings were confirmed at subsequent liver transplantation

On contrast-enhanced T1w images the enhancement patterns with gadolinium parallel those for enhanced CT examination, with many lesions enhancing early in the arterial phase (Fig. 14).

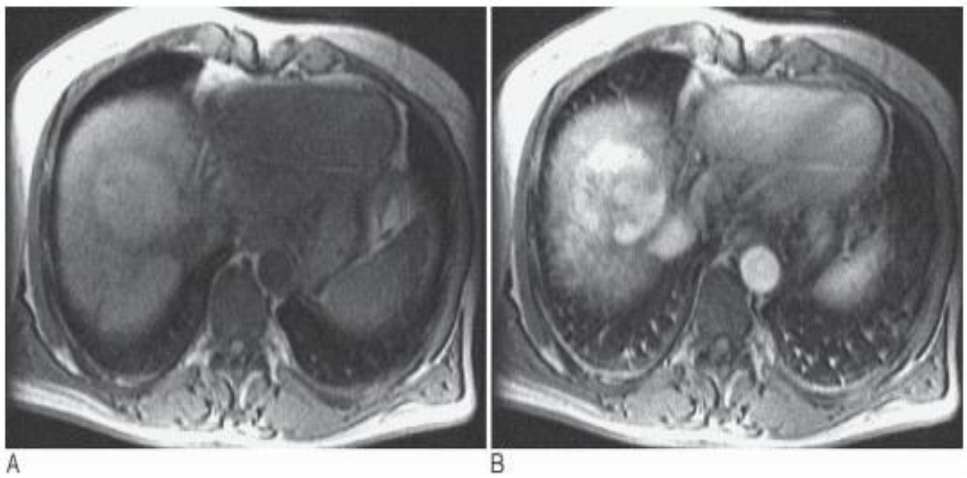

Figure 14: Hepatocellular carcinoma.

Dynamic T1w imaging (before (A) and (B) after IV gadolinium DTPA injection) can improve detection of hepatocellular carcinoma, particularly when optimal T2w imaging is unavailable or is degraded by artefacts.

Atypical regenerative nodules may cause some confusion, as they may also enhance in the arterial phase. Often these are of increased signal on T1w and low signal on T2w, due to iron accumulation allowing discrimination from HCC, but the presence of any heterogeneity should prompt further investigation and serial examinations may be necessary to monitor suspicious lesions. The presence of a low signal capsule on T1w is suggestive of malignant change. Radionuclide imaging, including FDG-PET, is relatively nonspecific for HCC and is not widely used for detecting or characterizing lesions. Angiography demonstrates dilated feeding arteries, abundant abnormal vessels and arteriovenous shunting, although some lesions may be relatively avascular. Portal vein invasion produces a 'threads and streaks' appearance highly suggestive but not specific for HCC. Angiography is used infrequently for the diagnosis of hepatoma but it can be helpful in preoperative assessment by defining the arterial and venous anatomy and evaluating the site and extent of portal or caval involvement when other techniques are unavailable or equivocal.

Angiography:

Angiography has been used as a diagnostic tool for HCC because of its highly vascular nature; however, the detection of tumors has been disappointing, particularly when <2 cm in diameter. At present angiography is more often used to define hepatic anatomy before resection or as guidance for transarterial chemoembolization therapy.

Liver biopsy(26) Histological confrmation is advisable in patients with large tumours who do not have cirrhosis or hepatitis B, in order to confrm the diagnosis and exclude metastatic tumour. Biopsy should be avoided in patients who may be eligible for transplantation or surgical resection because there is a small (< 2%) risk of tumour seeding along the needle tract. In all cases of potential HCC where biopsy is being considered, the impact that a confrmed diagnosis will have on therapy must be weighed against the risks of bleeding. If biopsy will not change management, then its appropriateness should be considered carefully.

Role of screening(26) Screening for HCC, by ultrasound scanning and AFP measurements at 6-month intervals, is indicated in highrisk patients, such as those with cirrhosis due to hepatitis B and C, haemochromatosis, alcohol, NASH and α1-antitrypsin defciency. It may also be indicated in individuals with chronic hepatitis B (who carry an increased risk of HCC, even in the absence of cirrhosis). Although no randomised controlled studies of outcome have been undertaken, screening identifes smaller tumours, often less than 3 cm in size, which are more likely to be cured by surgical resection, local ablative therapy or transplantation (Box 23.63). The role of screening in other forms of chronic liver disease, such as autoimmune hepatitis and PBC, is unclear. This is compounded by the fact that disease staging by biopsy is no longer standard practice in conditions such as PBC, so formal documentation of the presence of cirrhosis, which might be the trigger for commencement of HCC screening, rarely takes place.

CONCLUSION

Hepatocellular carcinoma (HCC) is the most common primary liver tumour, and the sixth most common cause of cancer worldwide. Serum alphafetoprotein (AFP) may be helpful in diagnosis and when markedly elevated may be diagnostic even in the absence of imaging confirmation. However, importantly HCC may occur with a normal serum AFP value. It remains unclear whether HCC arises from a regenerative nodule via a dysplastic intermediate state or as a de novo lesion. HCC can be solitary, multi-focal (in up to 40 per cent of cases in the Far East) or, rarely, diffuse. Larger lesions may demonstrate vascular invasive features, undergo haemorrhage and contain areas of thrombosis and necrosis, complicating the appearances on imaging. Hepatomas may also contain areas of fat. The above features are less frequently seen in smaller lesions (<3 cm). In cirrhotic livers current imaging techniques have limited sensitivity (60–80 per cent) for small hepatoma (≤1 cm) detection. Combinations of imaging modalities are often employed to detect small hepatomas, for example prior to liver transplantation. Imaging techniques are more sensitive at detecting HCC when the surrounding liver is normal. The 5-year survival of patients with HCC is approximately 30 per cent.

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