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Is a Liver Biopsy Necessary? Investigation of a Suspected Hepatocellular Carcinoma: A Pictorial Essay of Hepatocellular Carcinoma and the Revised American Association for the Study of Liver Disease Criteria

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Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and accounts for 80% of all liver tumours [1]. Worldwide, HCC is the fifth most commonly diagnosed cancer, and ranks as the fourth leading cause of cancer-related deaths [2,3]. Furthermore, the incidence rate of HCC has steadily increased over the past 3 decades within Canada and is projected to continue to increase over the next 10 years [2]. There are several well-established risk factors for the development of HCC, the most recognized being chronic hepatitis B and hepatitis C infection [3]. Hepatitis B carriers have been reported to have a relative risk of HCC, which is 100 times greater than the background population, and this figure is likely to be greater if there is established cirrhosis [4]. In fact, liver cirrhosis of any etiology, especially genetic hemochromatosis and alcohol-related cirrhosis, has been implicated in the development of HCC [3]. The incidence of HCC is higher among men, particularly in those who are from southeast Asia and Sub-Saharan Africa compared with women [3]. In North America, viral hepatitis, chronic liver disease that leads to cirrhosis, and, therefore, HCC are diseases that are predominant in large urban centres.

In addition to the assessment of risk factors and clinical presentation, the diagnosis of HCC typically relies on the use of imaging. However, due to the complex imaging presentation of cirrhosis, the diagnosis of HCC on the background of extensive fibrosis, regenerative nodule formation, and morphologic changes to the liver presents a challenge. As a result, clinicians may feel that histologic evaluation is necessary to make a definitive diagnosis. However, biopsy of a suspected HCC is not without risk. First, a biopsy is an invasive procedure that can cause pain and discomfort, and may require sedation to perform satisfactorily [5]. There also

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is the potential for creating a portal of entry for infection, or causing vascular injury, which can result in bleeding or the creation of an arteriovenous fistula.

Postprocedural hemorrhage is the most common serious complication of percutaneous liver biopsy, with rates that range from 0.3%-1.7%, and requires hospitalization [5–9]. Another significant concern is the potential for tumour seeding via local rupture of the tumour as a result of the biopsy itself, as well as tumour tract seeding along the path of the biopsy device or spillage of tumour into the peritoneum [3]. The rate of needle tract seeding during a percutaneous fine-needle biopsy of HCC has been reported to be in the range of 2%-3% (Figure 1) [3,10,11].

In July of 2010, the Practice Guidelines Committee of the American Association for Study of Liver Disease (AASLD) published an updated version of their guidelines that outlines the indications and recommendations for when biopsy is not indicated in patients with suspected HCC. The intent of this pictorial essay is to review these guidelines as well as to provide examples of the imaging characteristics associated with HCC.

Pathophysiology

The development of HCC in the cirrhotic liver is described either as de novo hepatocarcinogenesis or as a stepwise progression [12]. In the latter case, the development of a benign regenerative nodule may be the first step in the carcinogenesis of the liver [1]. This lesion may then further develop through phases from a low-grade dysplastic nodule to a high-grade dysplastic nodule to early HCC, in a multistep fashion [1]. A malignant transformation evolves within these lesions, there is a gradual reduction of normal hepatic arterial and portal venous supply, in conjunction with an increase in abnormal arterial supply [12].

A regenerative nodule represents a hepatocellular nodule that maintains its portal tracts and, thus, continues to receive its blood supply largely from the portal vein, with minimal contribution from the hepatic artery. In contrast, a dysplastic nodule demonstrates cellular dysplasia but does not meet histologic criteria for malignancy and is considered to be a premalignant lesion [12]. As the grade of malignancy within the nodule evolves, preferential neovascularization via the arterial supply increases secondary to tumour angiogenesis [12]. As a result, HCCs are typically supplied by abnormal neovascular arteries and, thus, demonstrate arterial hypervascularity [1]. Early HCCs have a variable degree of arterial and portal venous supply, whereas high-grade or poorly differentiated HCCs contain a large number of abnormal arteries (almost exclusively from the hepatic arterial supply) and a near absence of normal portal tracts (and, therefore, portal venous perfusion) [1]. This very important characteristic of HCC is one way that these lesions can be differentiated from regenerative nodules and dysplastic nodules on imaging.

The distinctive blood supply of HCCs can be displayed by using contrast enhanced imaging (ultrasound [US], computed tomography [CT], or magnetic resonance imaging [MRI]) to demonstrate a characteristic phenomenon known as ‘‘contrast washout.’’ This requires a multiphasic contrast-enhanced study, in particular, looking at the arterial and venous phases that allows for assessment of the vascularity

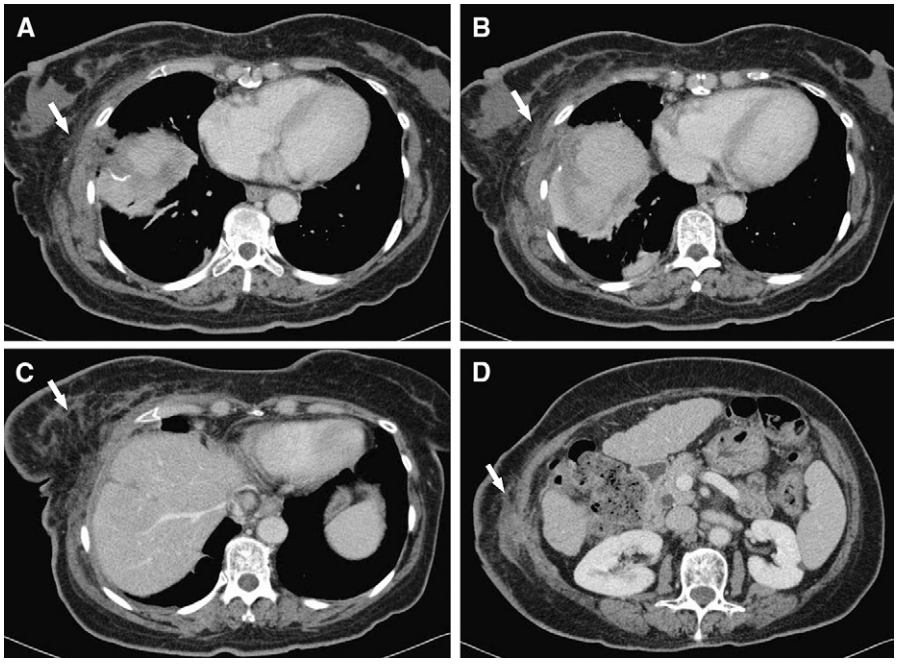

Figure 1. After needle biopsy of pathologically proven hepatocellular carcinoma (HCC), resulting in tumour tract seeding. Contrast-enhanced transaxial computed tomographic images on the portal venous phase, demonstrating soft-tissue changes within the right pleura (A), right hemithorax (B), musculature (C), and subcutaneous tissues (D) after needle biopsy of a liver mass, which was proven to be HCC on pathology. These changes, indicated by arrows, represent needle tumour tract seeding, which resulted in a significantly different surgical approach with wider resection margins.

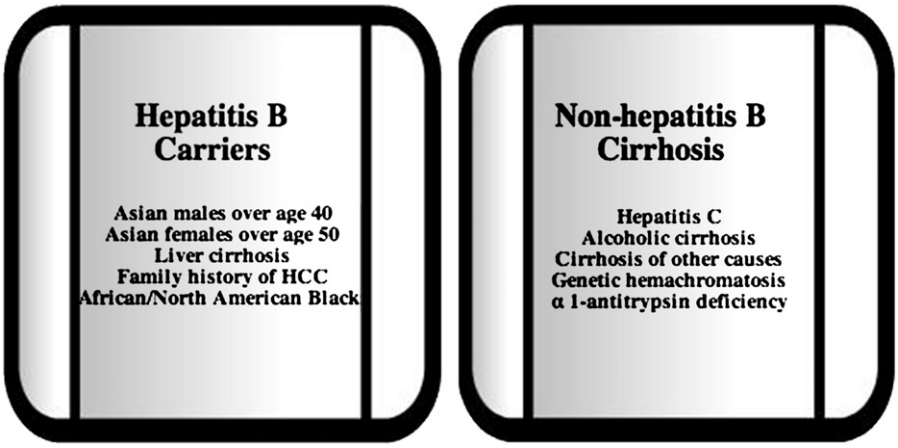

Figure 2. At-risk population in whom screening for hepatocellular carcinoma (HCC) is recommended.

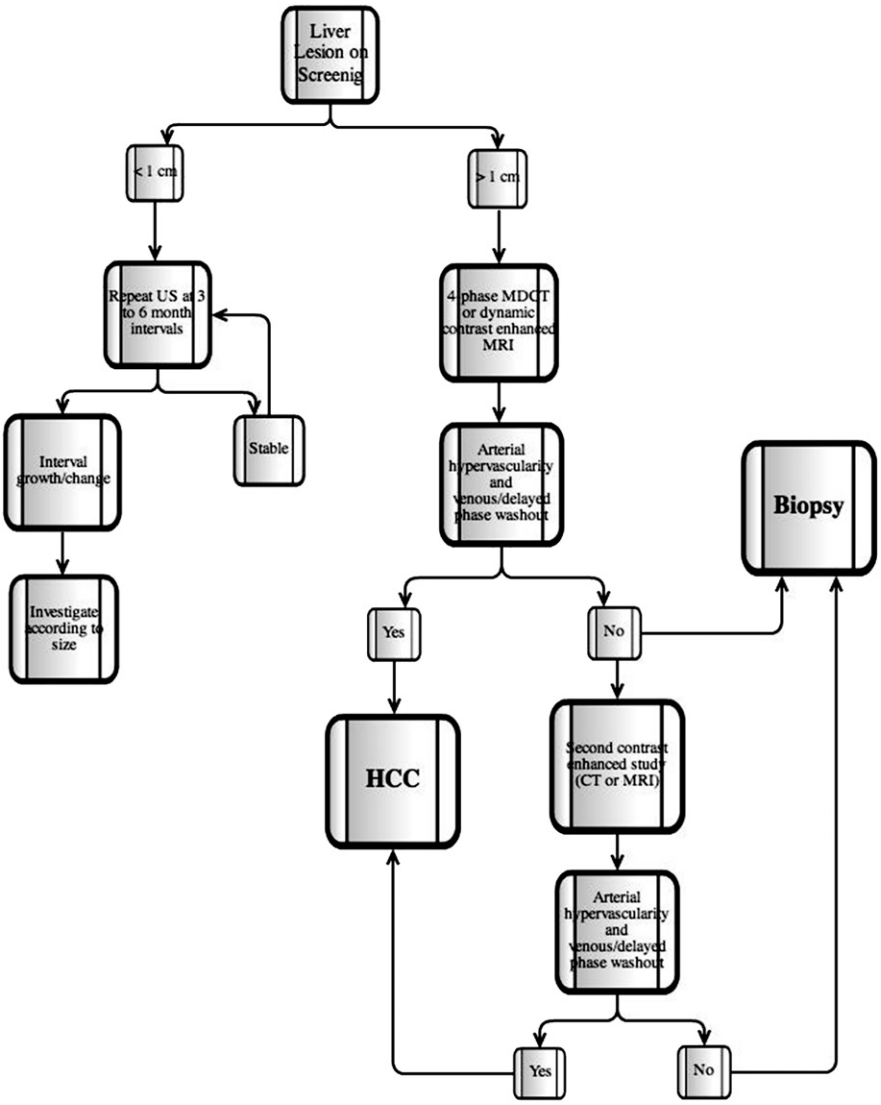

Figure 3. Algorithm outlining the investigation of liver nodules detected during screening. CT = computed tomography; HCC = hepatocellular carcinoma; MDCT = multidetector CT; MRI = magnetic resonance imaging; US = ultrasound.

of the lesion in question. During the arterial phase, HCC enhances more intensely compared with the surrounding liver parenchyma, because the process of vascular recruitment and angioneogenesis is almost exclusively drawn from the hepatic arterial supply, whereas the remainder of the liver is perfused by noncontrast enhanced portal venous blood [13]. Conversely, in the portal venous phase, contrast has ''washed out'' of the HCC lesion, whereas the surrounding liver parenchyma still receives contrast-enhanced blood via the portal system. Therefore, during the portal venous phase, HCCs enhance less intensely compared with the remainder of the liver. The finding of arterial contrast enhancement followed by portal venous washout is considered to be highly specific for the diagnosis of HCC [13].

Another characteristic feature of HCC is its tendency to invade and grow into the portal and hepatic veins and bile ducts, which results in the classic characteristics of macroscopic portal, hepatic, venous, and biliary invasion as demonstrated on imaging. This is in contradistinction to secondary liver malignancies and is a finding that can help distinguish HCC from liver metastases [1].

Screening

Screening is recommended for individuals who are considered at high risk for developing HCC. The at-risk populations for whom the efficacy of screening has been demonstrated are outlined in Figure 2 [13]. Screening tests for HCC fall under 1 of 2 categories, notably serologic and radiologic testing. The serologic marker that has best been studied in this regard is alpha-fetoprotein (AFP). Currently, an AFP cutoff value of $\geq$20 ng/mL is considered to provide the most optimal balance between sensitivity and specificity of this marker for the diagnosis of HCC [13]. However, this confers a sensitivity of only 60% for the detection of HCC, which means that 40% of cases would be missed on screening by using this cutoff value. Other cutoff values would have the inherent disadvantage of exceedingly high false-positive or false-negative results. Furthermore, AFP has been shown to be elevated in cases of intrahepatic cholangiocarcinoma, in some cases of colon cancer metastases, and it is well recognized that an AFP can be elevated on the basis of chronic viral hepatitis in the absence of HCC [14,15]. Therefore, AFP serology has fallen out of favor as a screening tool for HCC, with the most widely accepted tool for HCC surveillance in the at-risk population being US [13].

Approach to Diagnosis

According to the AASLD 2010 guidelines (updated 2010 AASLD Criteria), HCC can be diagnosed radiologically

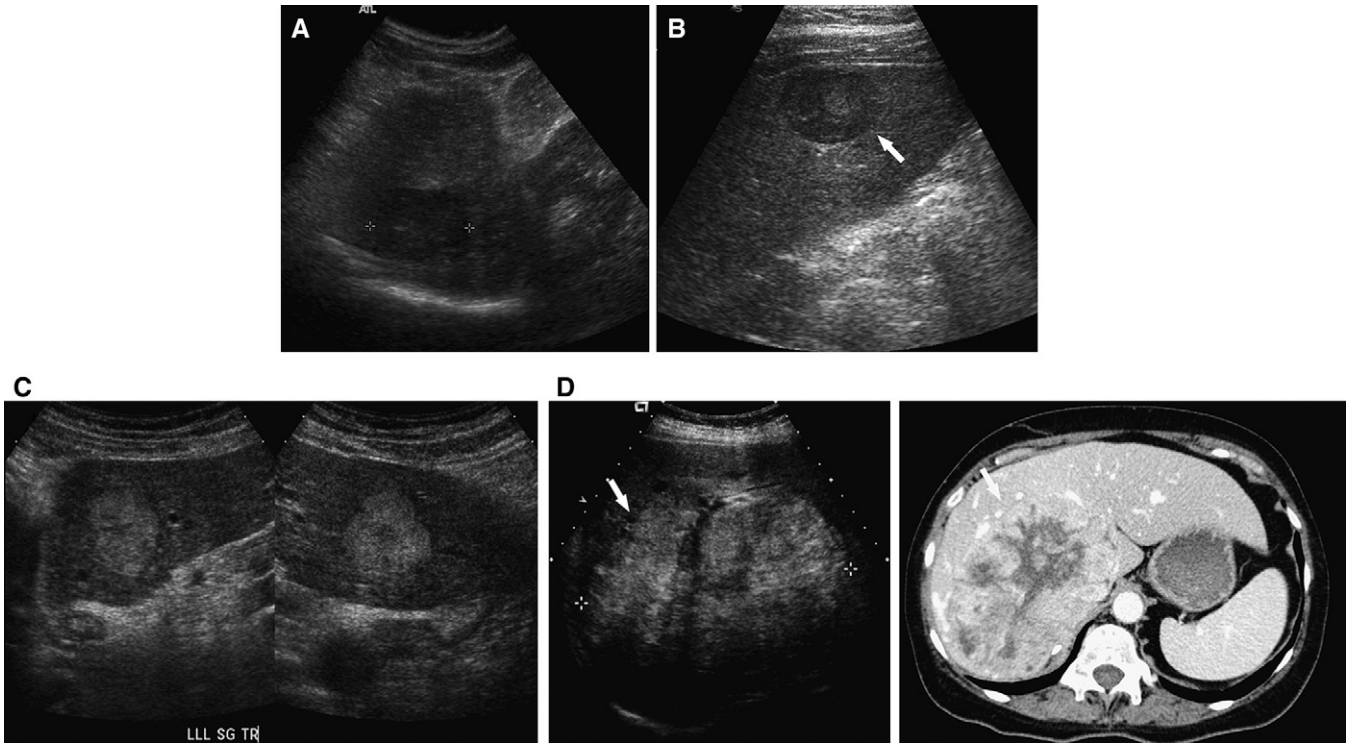

Figure 4. Characteristic ultrasonographic (US) findings of hepatocellular carcinoma (HCC). (A) A 51-year-old man with hepatitis C. Sagittal transabdominal US image, demonstrating a circular hypoechoic mass within the liver without posterior enhancement consistent with the characteristic US findings of HCC. (B) A 66-year-old man with hepatitis C. Transverse transabdominal US image, demonstrating a predominantly hypoechoic HCC with focal echogenic nodular deposit within it (arrow). (C) A 70-year-old woman with hepatitis B. A further example of focal HCC, demonstrating increased echogenicity. (D) Large heterogenous, predominantly hyperechoic mass (arrow) within the liver, with internal hypoechoic architecture, demonstrating the tendency for larger HCCs (>3 cm) to have a propensity towards internal necrosis. The accompanying contrast-enhanced transaxial computed tomography of the same patient, illustrating the internal necrotic characteristics of the HCC (arrow).

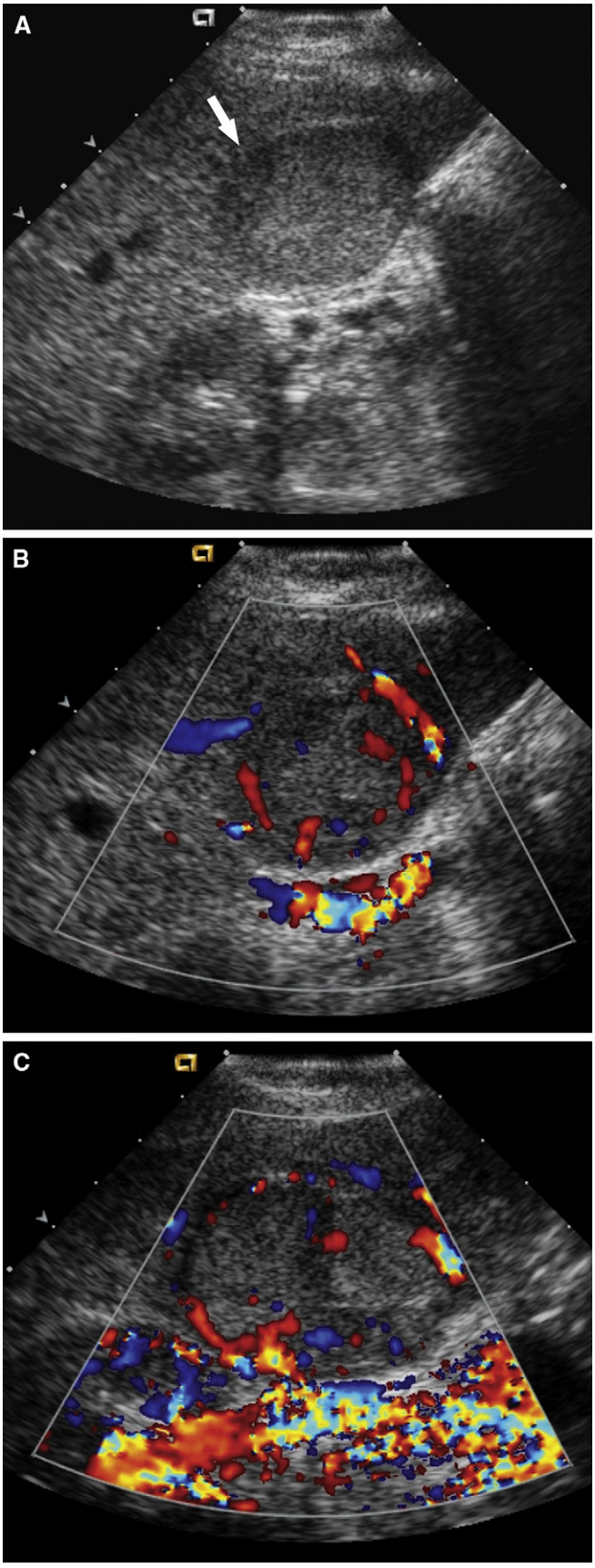

Figure 5. Hepatocellular carcinoma (HCC) on Dopppler imaging in a 70-year-old woman with hepatitis C. (A) Transverse transabdominal ultrasound (US), showing a well-circumscribed rounded mass (arrow) of mixed echogenicity bulging the surface contour of the left lobe of the liver. (B, C) Colour Doppler US, demonstrating interval vascularity within the tumour as well as a peritumoural hypervascular ring, giving the characteristic "basket pattern." This figure is available in colour online at http://www.carjonline.org/.

without the need for biopsy, provided that certain typical and diagnostic features are present on imaging. The major difference between the previous (2005) and current AASLD guidelines involves the exclusion of the 1-2–cm size category and the corresponding use of 2 contrast-enhanced diagnostic tests to confirm HCC. Results of several studies have provided external validation that the typical appearances of arterial hypervascularity and venous washout within this subgroup are so highly specific that only a single study is necessary if these appearances are present [13]. Furthermore, contrast-enhanced US has been omitted from the updated guidelines in the diagnosis of HCC. This decision was based on concerns regarding reports of false-positive results for HCC in patients with biopsy proven intrahepatic cholangiocarcinoma [13].

The most current algorithm for the investigation of nodules found on screening US for at-risk populations is summarized in Figure 3 [13]. Lesions that measure <1 cm are generally considered to have a low probability of being HCC [3]. However, given the potential for carcinogenesis over time, the guidelines propose that a close follow-up regimen be initiated. This consists of US follow-up at 6-monthly intervals in high-risk populations, the finding of a new nodule or an enlarging mass, even if previously considered benign, requires further evaluation [13]. Lesions that are >1 cm should be further investigated with either a 4-phase multidetector CT, or dynamic contrast-enhanced MRI. Of note, the AASLD criteria do not designate which study is to be used initially and which to use for follow-up. If there is arterial hypervascularity and portal venous or delayed-phase contrast washout, as previously described, the diagnosis of HCC can be made. If the findings are not characteristic of HCC based on the aforementioned criteria, 1 of 2 approaches may be followed. An alternate contrast study can be performed, which, if consistent with the typical appearance of HCC, confirms the diagnosis. Alternatively, the clinician may choose to biopsy the lesion at this point. If the results of the second imaging study are not consistent with HCC, then a biopsy should be performed.

If a lesion is biopsied based on the AASLD recommendations, but histopathologic analysis is negative for HCC, then the lesion should be followed up radiologically at intervals of 3-6 months until the lesion disappears, enlarges, or displays the diagnostic appearance of HCC [13]. There currently are no data to establish the best follow-up policy, but the AASLD guidelines recommend repeated biopsy or follow-up CT or MRI to detect further growth. If the lesion enlarges but remains atypical for HCC, then repeated biopsy is recommended [13].

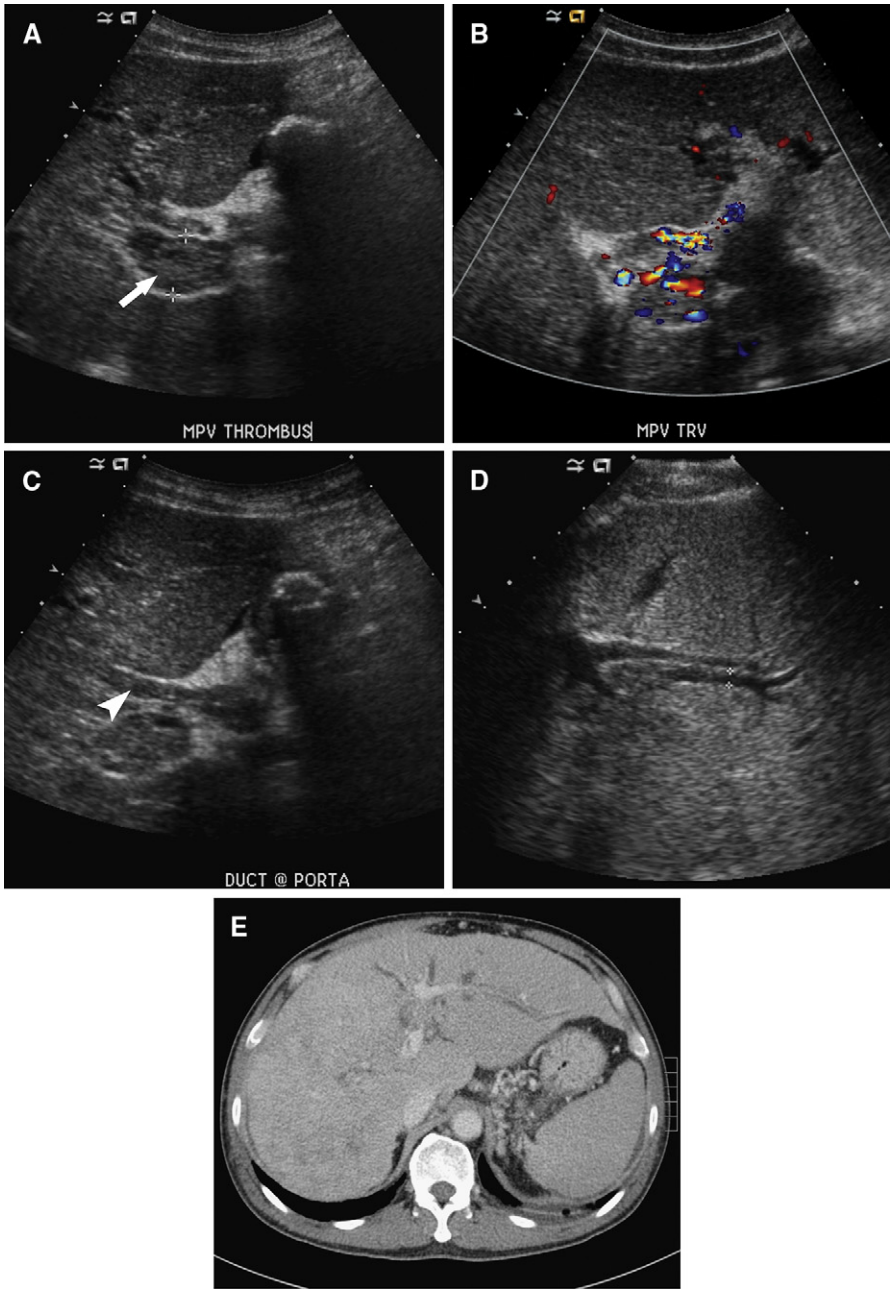

Figure 6. Additional findings on ultrasound (US) consistent with hepatocellular carcinoma (HCC). (A, B) Tumoural thrombus is located within the main portal vein (arrow). Colour Doppler US, demonstrating flow within the thrombus, indicating tumoural thrombus rather than bland thrombus. (C) Echogenic material is identified within the common bile duct (arrowhead), consistent with tumoural invasion. (D) Transverse transabdominal US, showing intrahepatic biliary duct dilatation. (E) The contrast-enhanced transaxial computed tomography, demonstrating a hepatic mass and exhibiting mass effect, and compressing on the adjacent biliary ducts and resulting in intrahepatic biliary duct dilatation. This figure is available in colour online at http://www.carjonline.org/.

US

US is a primary technique for imaging the liver, biliary tree, and gallbladder. Furthermore, US has a reported sensitivity and specificity of 60%-80% and >90%, respectively, for the detection of HCC [13]. The appearance of HCC is variable, depending on lesion composition and size. Most small HCCs (<3 cm) generally appear as slightly hypoechoic nodules, without posterior enhancement, within a background of a heterogenous-appearing cirrhotic liver (Figure 4A) [16,17]. HCCs also can appear hyperechoic due to fatty deposition, sinusoidal dilatation, or fibrosis, which can make them difficult to distinguish from a cavernous hemangioma or focal fatty deposition (Figure 4, B and C) [16]. Lesions >3 cm have a tendency towards internal necrosis and show a more heterogenous pattern of echogenicity (Figure 4D) [17].

Doppler US is useful in demonstrating the presence of arterial hypervascularity within the tumour as well as the typical morphology of intra- and peritumoural vessels, referred to as the ‘‘basket pattern’’ (Figure 5) [1]. Power Doppler US, which registers the amplitude of Doppler shifts

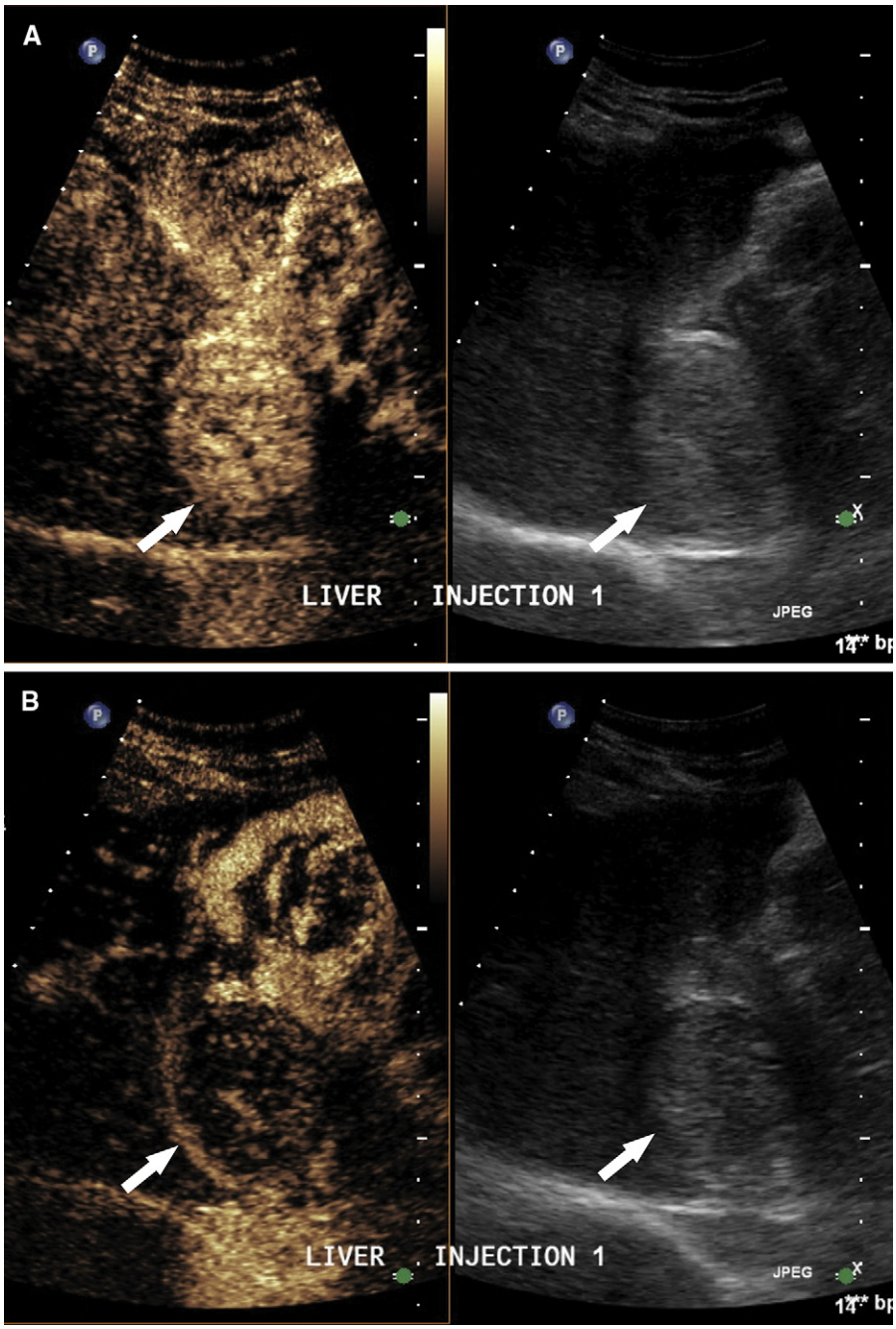

Figure 7. Contrast enhanced ultrasound of a 59-year-old man with hepatocellular carcinoma (HCC). (A) Sagittal contrast-enhanced of a liver mass, demonstrating enhancement during the arterial phase of the study (arrows). (B) This mass exhibits the characteristic washout on the portal venous phases, consistent with HCC (arrows).

rather than the velocity, is considered more sensitive than Doppler US for the detection of small vessels and flow within tumours [16,17]. Other findings on US consistent with a diagnosis of HCC include portal or hepatic venous thrombosis, displacement or compression of the intrahepatic blood vessels, or segmental bile duct obstruction (Figure 6) [17]. However, delineation of these findings is often challenging.

It also is possible to demonstrate arterial enhancement and portal venous washout of HCC with the aid of US contrast agents (Figure 7). These agents are typically solutions of coated microbubbles that act as acoustic reflectors and appear echogenic on US imaging [16–18]. In the setting of the AASLD guidelines, there is no current role for contrast-enhanced US due to the unavailability in the United States [18]. Given the impending regulatory approval of several new agents, contrast-enhanced US will likely be incorporated into subsequent iterations and revisions.

CT

A multiphasic multidetector CT can systematically evaluate the liver parenchyma, hepatic arteries, hepatic veins,

and portal veins. The 4 phases used are precontrast, arterial, portal venous, and delayed or equilibrium phases. In the nonenhanced phase, siderotic regenerative nodules show higher attenuation than the surrounding liver parenchyma, and, thus, this study phase is useful to ensure that these nodules are not mistaken for enhancing nodules in the arterial phase [17]. Small HCCs are well defined with smooth encapsulated margins, however, large diffuse infiltrative lesions with poorly defined margins (especially those with frank venous invasion) are also described [17].

In the arterial phase, the typical HCC shows intense enhancement as a result of hypervascularity secondary to tumour neoangiogenesis [16,17]. The fibrous capsule has no marked enhancement during this phase. Tumour thrombosis may also be visualized during this phase and can be distinguished from benign thrombosis, which does not demonstrate contrast enhancement [17]. During the portal venous phase, HCC shows contrast washout and, therefore, appears as a hypoattenuating lesion relative to the surrounding liver parenchyma (Figure 8) [16,17]. At the same time, the fibrous capsule shows gradual enhancement [17].

In the delayed phase, HCC continues to appear as a hypoenhancing lesion within the liver parenchyma. Conversely, the fibrous capsule typically retains contrast medium and, therefore, appears hyperdense [17]. According to some researchers, small HCCs (<3 cm) are most easily visualized during the delayed phase scan and appear hypodense compared with liver parenchyma [19,20]. The use of multidetector CT allows for a comprehensive assessment of any metastatic spread to periportal or retroperitoneal lymph nodes (Figure 9) or to the peritoneal cavity [16].

MRI

Multiphasic gadolinium-enhanced T1-weighted MRI of HCC demonstrates findings that are similar to those found on multiphasic contrast-enhanced CT, namely arterial phase hypervascularity and portal venous or delayed phase contrast washout (Figure 10) [1,16,17]. HCC displays variable signal intensity on T1-weighted scans. Well-differentiated HCCs may appear as high-intensity nodules compared with the surrounding liver parenchyma, in part, due to the fatty content of these tumours as well as the presence of copper, glycogen, or zinc in the surrounding parenchyma (Figure 11 and Figure 12, E and F) [1,12,16], which is in contrast to the more poorly differentiated tumours, which commonly have lower signal intensity on T1-weighted imaging [1,16].

HCC typically appears as a higher signal intensity nodule on T2-weighted scans [12,16,17]. In fact, a hyperintense nodule seen within a cirrhotic liver on T2-weighted imaging is considered to be highly suggestive of a malignancy [1]. The fibrous capsule appears as a low signal rim on both T1- and T2-weighted images [1].

Regenerative nodules are typically isointense on both T1- and T2-weighted images and do not enhance during the arterial phase on a contrast-enhanced study (Figure 12, A-D) [17,21]. Less commonly, they may appear hyperintense on T1-weighted imaging due to the presence of lipid, protein, or, possibly, copper [12]. Furthermore, siderotic regenerative nodules may appear hypointense on both T1- and T2-weighted images [12]. As a general rule, dysplastic nodules display the same MRI characteristics as regenerative nodules [12]. Some HCCs may demonstrate hyperintensity on T1-weighted images and hypointensity on T2-weighted images, and, therefore, can mimic regenerative and dysplastic nodules [12]. In such cases, arterial phase hypervascularity remains a distinguishing feature [12].

Two entities that should be noted include the occurrence of HCC within a dysplastic nodule, and the hypovascular HCC. The appearance of a dysplastic nodule with a central focus of HCC was first described on T2-weighted images and has been coined ‘‘a nodule within a nodule’’ (Figure 12, E-H) [12], which appears as a hyperintense focus, which may also demonstrate arterial phase enhancement, which occurs within a low-signal-intensity nodule on T2-weighted images [12]. Hypovascular HCCs have also been described as a rare

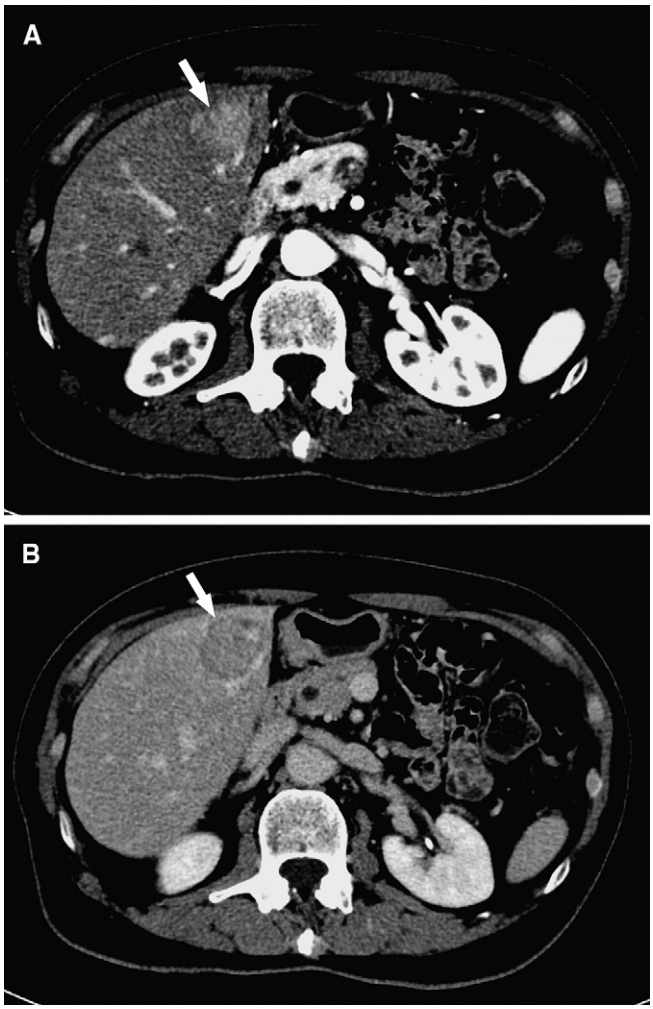

Figure 8. Characteristic computed tomographic (CT) findings of hepatocellular carcinoma (HCC). (A) Transaxial contrast-enhanced CT on the arterial phase, illustrating a hyperenhancing liver mass (arrows). (B) The portal venous phase highlights the washout of the mass to hypoattenuating in comparison with the surrounding liver parenchyma, characteristic for an HCC.

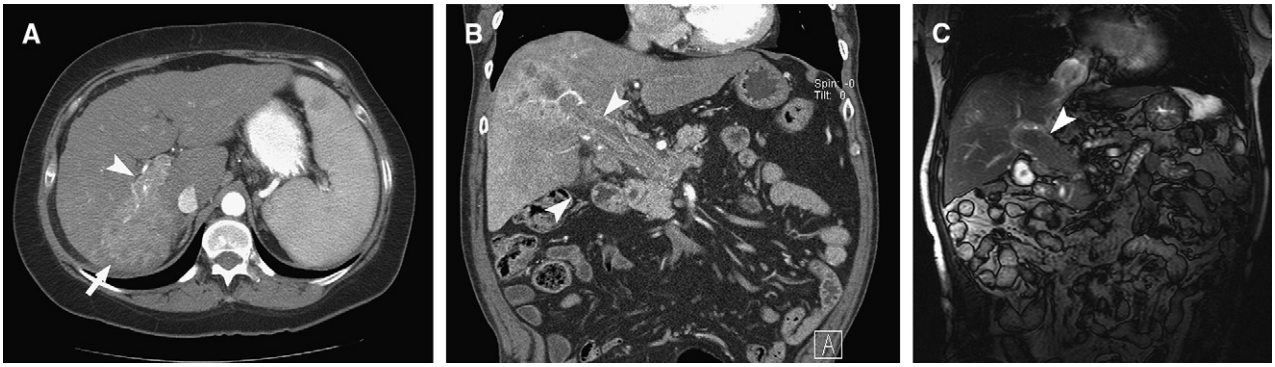

Figure 9. (A) Contrast-enhanced transaxial computed tomography (CT) on the arterial phase, demonstrating a hypervascular hepatocellular carcinoma (HCC) (arrow) within liver segments 5/6, which invades into the right portal vein (arrowhead). (B) Coronal contrast-enhanced CT of the same patient with tumoural invasion into the main portal vein (arrowheads). (C) Corresponding coronal fast imaging employing steady-state acquisition sequence with tumoural invasion of the main portal vein (arrowhead).

entity and likely represent the stage of carcinogenesis within a nodule where there has been partial or complete loss of the normal portal tract, without the associated increase in arterialization to demonstrate arterial hypervascularity. These lesions, therefore, will appear isointense or hypointense in the arterial phase [12].

Typically, gadolinium chelates are used for MRI contrast media. More recently, hepatocyte-targeted and reticuloendothelial system targeted compounds, have become available, which allows for a wider range of tissue signal manipulations [17,22].

Two hepatobiliary-targeted compounds are currently in clinical usage: gadobenate dimeglumine (MultiHance; Bracco Imaging, Montreal, QC) and gadoxetic acid (Gd-EOB-DTPA; Primovist; Bayer Schering Pharma, Toronto, ON) [17]. These agents are taken up by normal hepatocytes and, therefore, allow both the visualization of vasculature as well as hepatobiliary excretion [22]. Because hepatomas do not have conventional hepatic microarchitecture and an absence of both functional biliary ducts and Kupffer cell lines, these alternative contrast media can be used for the characterization of liver lesions. Well-differentiated and

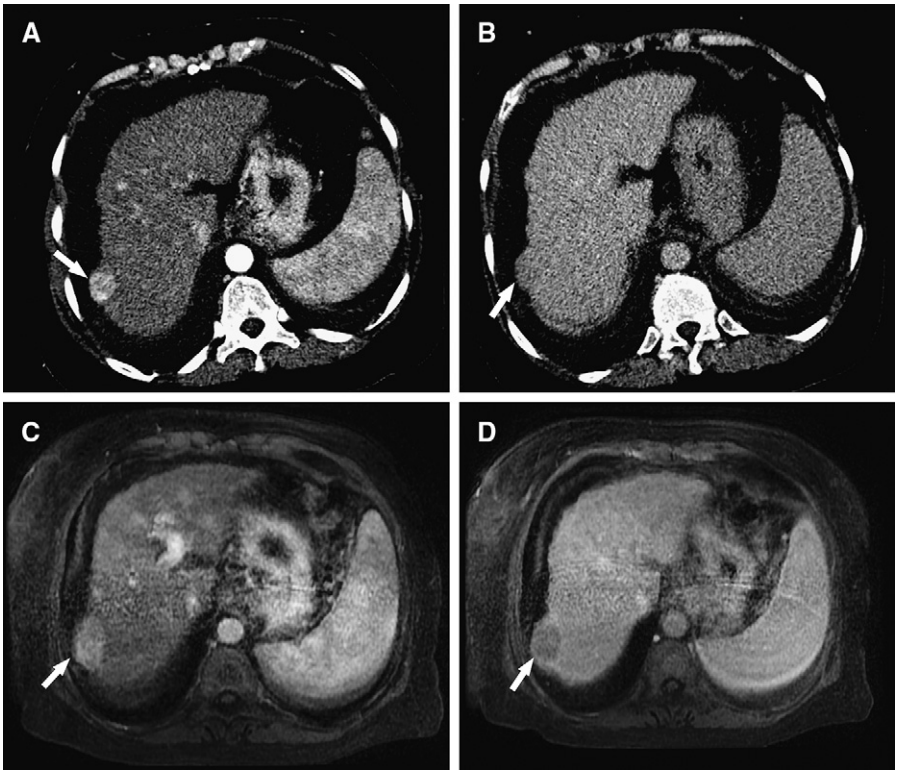

Figure 10. (A) A 60-year-old woman with hepatitis C and liver cirrhosis. Contrast-enhanced transaxial computed tomography with a liver mass (arrows), demonstrating arterial enhancement and subtle washout to hypoattenuating to the liver parenchyma on the portal venous phase (B). (C) Gadolinium-enhanced liver acceleration volume acquisition magnetic resonance imaging sequences with corresponding arterial enhancement and washout on the portal venous phase of the liver mass (arrows) (D).

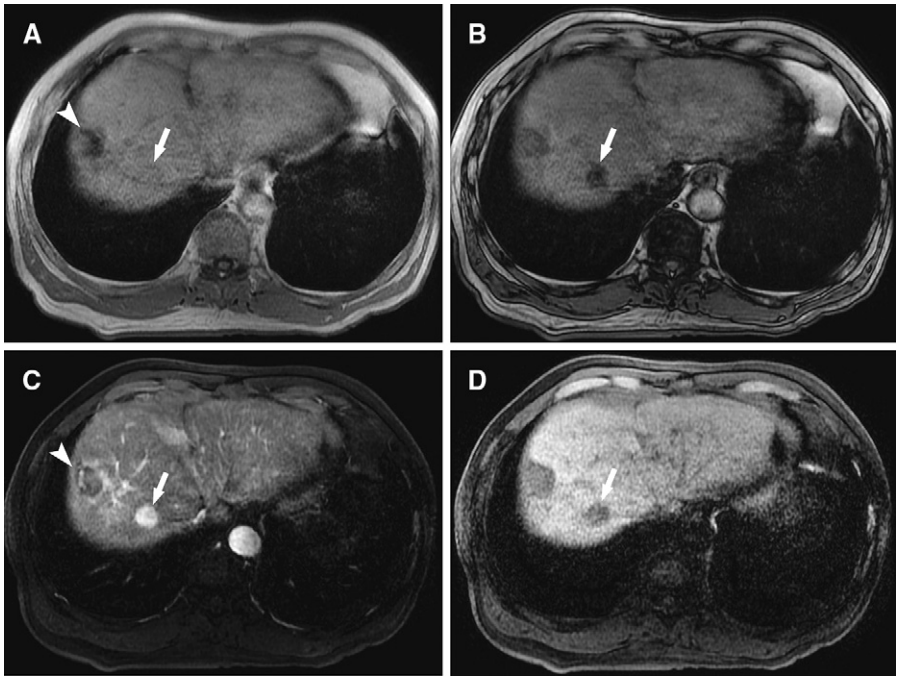

Figure 11. (A) Axial gradient echo T1 in phase sequence with an isointense mass located in segment 7, exhibiting signal intensity drop out on out-of-phase sequence (B) consistent with intracytoplasmic fat (arrows). There is an additional hypointense mass located within the lateral aspect of segment 7 (arrowheads). (C) Gadolinium-enhanced liver acceleration volume acquisition magnetic resonance image during the arterial phase, which demonstrate hypervascularity of the mass (arrows) with corresponding washout on the portal venous phase (D). The additional lesion (arrowheads), showing progressive centripetal filling throughout the phases (not all images shown) consistent with a cavernous hemangioma.

moderately differentiated HCCs often retain a sufficient volume of hepatocytes to take up these compounds, whereas poorly differentiated lesions do not. Therefore, low-grade HCCs enhance more intensely compared with high-grade lesions [23].

Alternatively, reticuloendothelial system–targeted compounds, also known as superparamagnetic particles of iron oxides, cause distortion of local magnetic fields and result in signal loss on T2-weighted images [17]. Kupffer cells within normal liver parenchyma take up more than 80% these agents and, therefore, exhibit signal drop out [17]. In contrast, poorly differentiated HCCs and metastasis do not take up these agents and, therefore, appear relatively hyperintense [17]. It should be noted that these agents are not currently approved for use in Canada.

Discussion

The rising incidence of viral-associated hepatitis in Canada has resulted in an increased incidence of HCC. Recent estimates indicate that as of December 2007, approximately 242,500 Canadians have been infected with hepatitis C virus, which corresponds to a prevalence rate of 0.7% (R. Remis, unpublished data, 2009), and translating into an estimated 2.2 per 100,000 in 2008. Countries of highest endemic incidents are located in Africa, Latin America, and Central and Southeast Asia, where, in these regions, prevalence rates of 5%-10% are frequently reported [24].

Although the reported number and corresponding rates of hepatitis B are decreasing, primarily due to immunization, chronic hepatitis B remains a public health concern worldwide. It is estimated that 2 billion people worldwide have serologic evidence of past or present hepatitis B infection, and 360 million are chronically infected and at risk for hepatitis B–related liver disease. Approximately one-third of all cases of liver cirrhosis, and half of cases of HCC can be attributed to chronic hepatitis B infection, with approximately 5%-6% of the population developing HCC [25]. The sequelae of chronic hepatitis B infection results in a public health concern that will extend decades beyond the initial incidence. When combined, it is estimated that between 500,000 and 600,000 Canadians have been infected with hepatitis B or C [26]. Current models predicted that 1565 new cases (1132 men, 433 women) and 802 deaths (654 men, 148 women) of HCC are expected to occur in Canada in 2010 [27]. With the increasing trend towards horizontal transmission, particularly with hepatitis C virus, improved population-based surveillance in the context of cost-effective screening and diagnosis is paramount.

The AASLD criteria, revised as of July 2010 provides an evidence-based consensus as to the most appropriate next step in the management of a suspicious lesion in the at-risk population. Compared with previous AASLD criteria, the algorithm is significantly simplified and requires demonstrable early arterial enhancement and early washout in a single multiphase examination for the diagnosis of HCC. Inferred from this algorithm, and perhaps most important, is

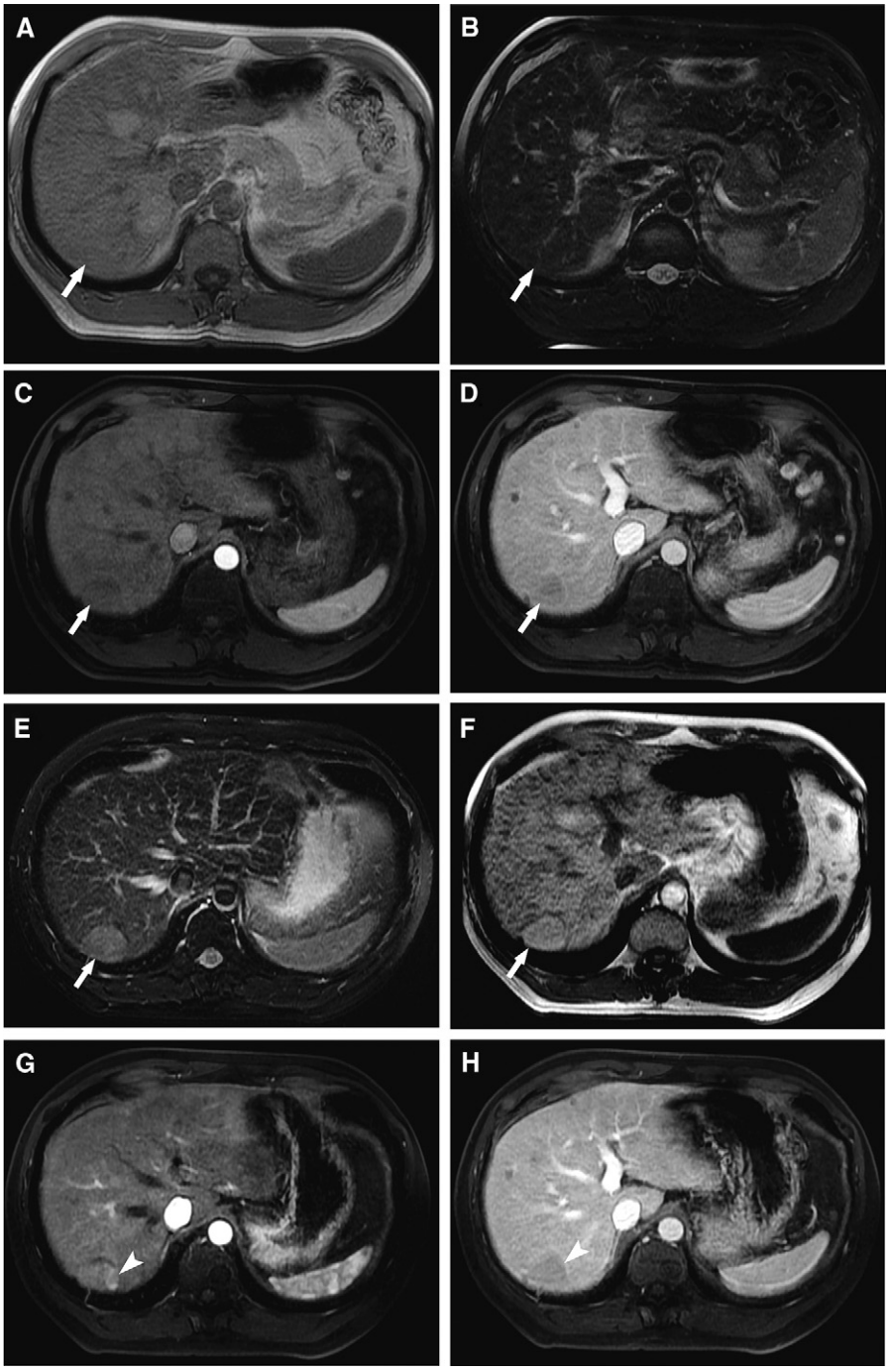

Figure 12. (A) Axial gradient echo T1 out-of-phase image, demonstrating a subtle isointense lesion (arrows) within segment 6, which, on the T2-weighted sequence, is also isointense to the liver parenchyma (B). (C) Gadolinium-enhanced liver acceleration volume acquisition (LAVA) magnetic resonance imaging (MRI) during the arterial phase, making the lesion (arrows) slightly more conspicuous but does not demonstrate enhancement on this phase, nor the portal venous phase (D), and is consistent with a regenerative nodule. (E) T2-weighted MRI sequence on 1-year follow-up with the segment 6 lesion (arrow) now hyperintense compared with the liver parenchyma. (F) Axial gradient echo T1 in phase image, demonstrating that the nodule is now of increased signal intensity. (G) Gadolinium-enhanced LAVA MRI sequence, demonstrating a focus of nodular arterial enhancement along its medial aspect (arrowheads) consistent with the ''nodule in nodule'' appearance. This focus washes out and is hypointense to liver parenchyma on the portal venous phase (H), consistent with a focus of malignant transformation within this nodule.

the trend towards a radiographic diagnosis as opposed to a histopathologic diagnosis (biopsy).

In the high-risk population, as defined in the AALSD criteria, the indications for continued enhanced follow-up is warranted. As per the guidelines, the epidemiologic and economic impact of appropriate surveillance is based upon the availability of imaging (the guidelines are intentionally nonspecific as to the initial modality of assessment, beyond

US) and the potential risk to the patient, bearing in mind as low as reasonably acceptable (ALARA) principles. Although the current guidelines do not take into account the inherent risks of cumulative radiation exposure, the societal impact of failure to diagnose early presenting and potentially curable disease currently outweighs the risk of high-frequency follow-up imaging. As previously discussed, the risk of complication, tumour seeding, tumour rupture, and associated cost of biopsy warrants a conservative approach to biopsy of lesions that meet AASLD criteria and/or demonstrate classic imaging characteristics within the at-risk population, as illustrated by this pictorial review.

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