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Hepatocellular carcinoma—issues in imaging

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Abstract

The imaging diagnosis of hepatocellular carcinoma is challenging as benign hypervascular lesions and arterioportal shunts (pseudolesions) often mimic it. There is also overlap in the imaging appearance from dysplastic and regenerating nodules. This article addresses the above imaging problems, examines proposed non-invasive imaging criteria for the diagnosis of hepatoma and discusses the optimal imaging modality.

Keywords: *CT; MR; US; microbubble; hepatocellular carcinoma.*

Introduction

Hepatoma, or hepatocellular carcinoma (HCC), is an epidemiologically significant tumor worldwide. It is the fifth most common tumor in the world[1]. It is particularly prevalent in Asia where hepatitis B infections are endemic. HCC has generated interest in Europe and the USA as its incidence has increased in the past decade. Several articles have reviewed the imaging features of HCC[2–8]. This review aims to provide a succinct summary of the issues confronting the radiologist in the assessment of HCC.

Surveillance

Ultrasonography (US) is a widely accepted imaging modality for HCC screening that is cheap, safe and repeatable. Due to its widespread adoption, it is difficult to recruit patients into a non-screening arm of a randomized trial. To date, there are no randomized controlled trials to validate the value of US in screening for HCC. In a large study employing both US and serum alpha fetoprotein (AFP) involving 1069 non-cirrhotic hepatitis B carriers, 14 HCC were detected. US had a sensitivity of 78.8% and specificity of 93.8%[9]. In general, HCC detection rates of surveillance are between 2 and 10% depending on the length of follow-up[10]. The mean doubling time of HCC on US is 180 days and hence 6 months is a reasonable screening time interval[11–13].

A consensus statement from the European Association for the Study of the Liver (EASL) suggested surveillance based on AFP and US every 6 months[14]. It is recommended that only patients who would benefit from surgery be screened. Hence screening is suggested for non-cirrhotic patients and Child–Pugh's A cirrhotic patients. Child–Pugh's B cirrhotics would benefit from screening if transplantation was available. Child–Pugh's C cirrhotics should be considered for transplantation and if this is not available, surveillance is pointless.

The positive predictive value of US is low (14%) and hence there is a need for recall and work-up protocols[15]. Such a strategy was proposed by the EASL[14]. The suggested work-up protocol relies on the size of the nodule detected. Nodules less than 1 cm are deemed too small to be accurately evaluated and three monthly US is suggested to assess nodule growth. For nodules larger than 2 cm in a patient with cirrhosis, a presumptive diagnosis of HCC is made based on non-invasive criteria elaborated in a later section. For cirrhotics with nodules between 1 and 2 cm, fine-needle aspiration cytology is

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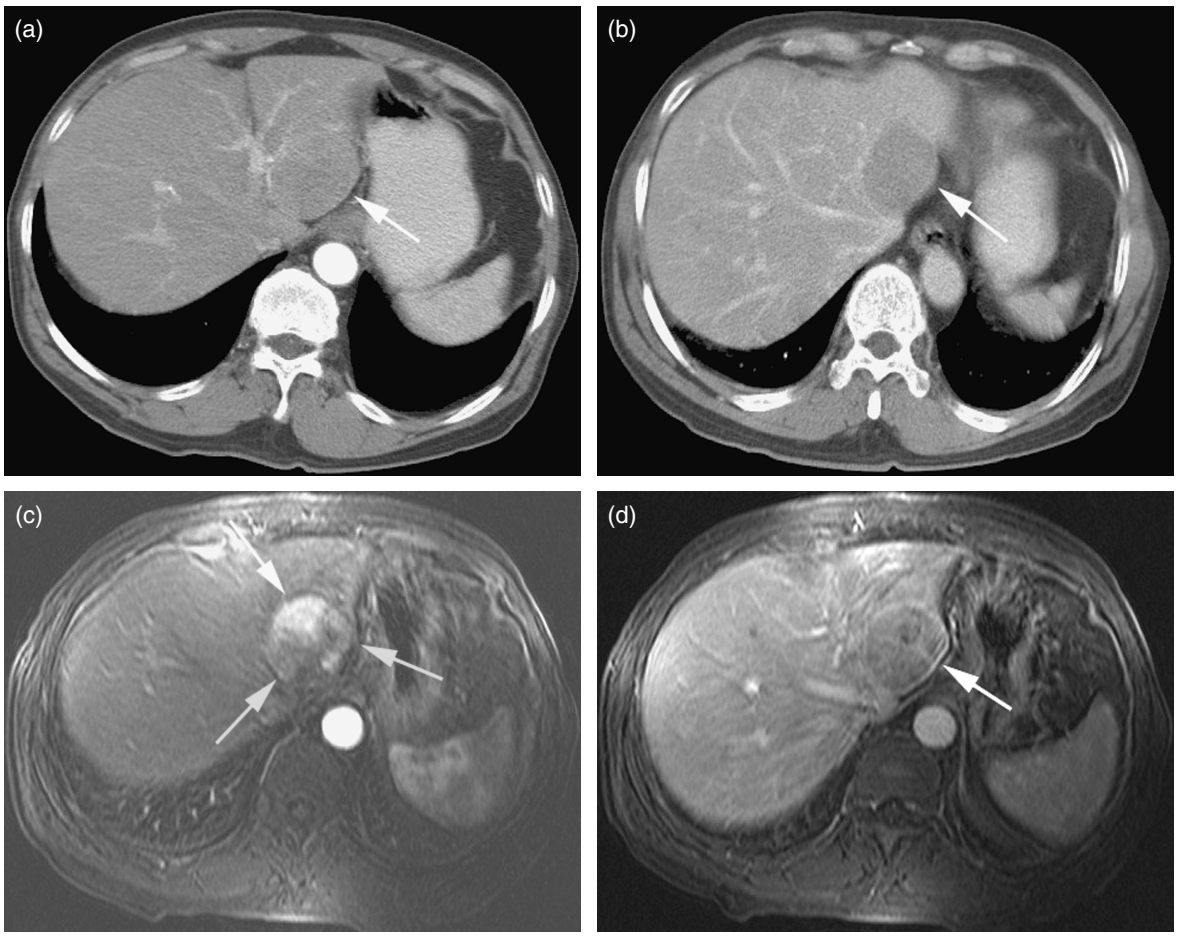


Figure 1 **HCC. (a) Arterial phase helical CT shows a minimally hyperdense lesion (arrow). (b) Portal venous phase helical CT shows that the lesion has faded and an enhancing pseudocapsule is noted (arrow). (c) Arterial phase T1-weighted fat-suppressed 3D gradient-echo scan shows enhancement of the lesion better than CT. Note that the lesion is predominantly composed of three lesions enhancing to different degrees (arrows), 'tiled' together like a 'mosaic'. Note that MR shows the mosaic pattern of HCC better than CT. (d) Portal venous phase T1-weighted fat-suppressed 3D gradient-echo scan shows that there is an enhancing pseudocapsule encircling the mosaic of 'tiles' and the confluent portions of each nodule form a triangularly shaped enhancing fibrous septa (arrow). Note that MR shows the pseudocapsule and fibrous septa better than CT. (Reproduced with permissions from Thng CH, Kuo Y, Blomley MJ. Imaging hepatocellular carcinoma. Cancer Rev Asia-Pacific 2003; 1: 191.)**

suggested. However, needle biopsy is not recommended if the lesion is surgically curable. Spiral or multidetector computed tomography (CT) is suggested to evaluate patients with elevated AFP but negative US examination.

Imaging characteristics of HCC

HCC is a hypervascular tumor with increased angiogenetic supply and hepatic arterial supply. It has a pseudocapsule composed of collagenous fibers and a layer of compressed liver tissue. Classically the tumor demonstrates hepatic arterial enhancement. During the portal venous and equilibrium phases, the tumor fades off while the pseudocapsule enhances brightly[7]. HCC often shows a mosaic pattern composed of several nodular components placed together like mosaic tiles. The mosaic pattern may be related to the multiclonal nature of the tumor[16]. Each nodular component can be thought of as arising from a clone of tumor cells with its own pseudocapsule. When two or more nodular components meet, their common boundary would form the internal septae, which would also enhance in the portal venous phase, just like the pseudocapsule (Fig. 1).

The above gross pathological features form the basis of imaging for HCC and are exploited by the various modalities. The pseudocapsule and internal septa are seen grossly in 80% of hepatomas[17]. They are more commonly seen in larger tumors (Fig. 2). On magnetic resonance (MR) scans, the pseudocapsule is seen in 67%, the internal septa in 43% and the mosaic appearance in

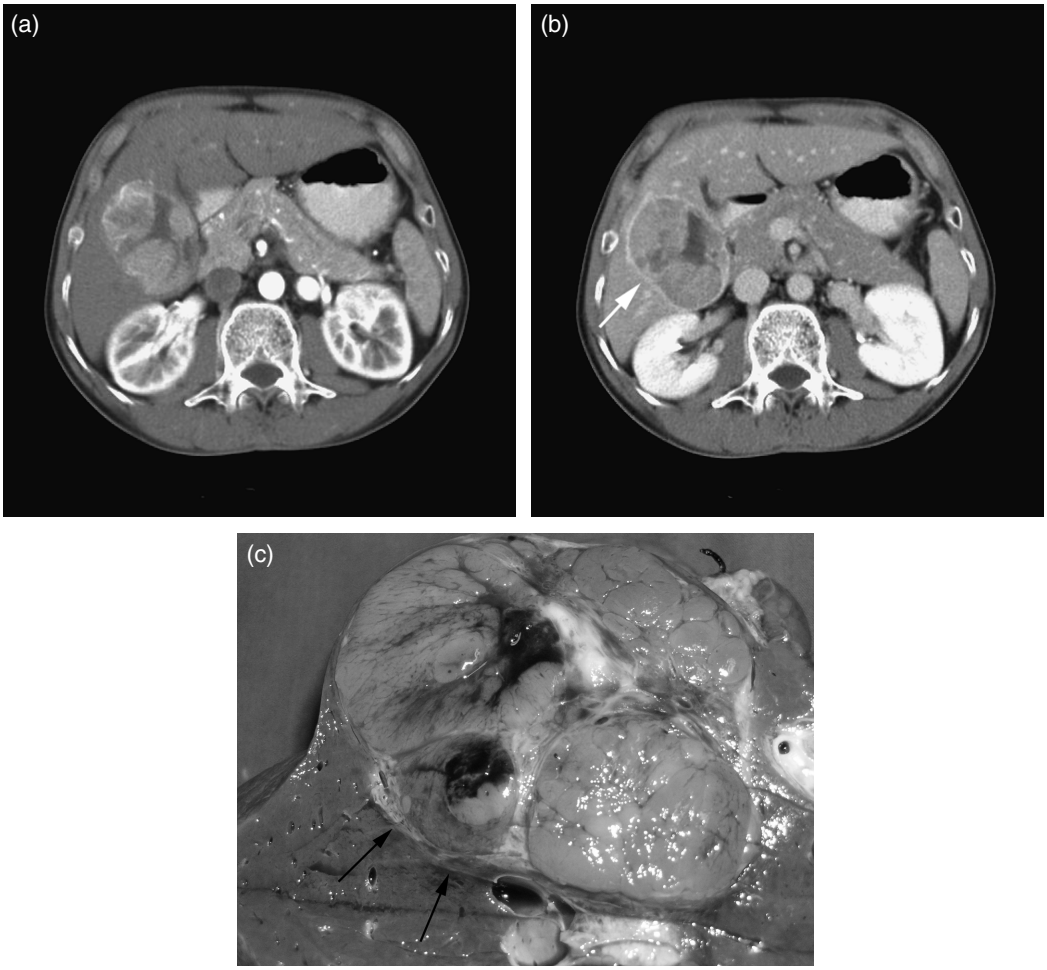


Figure 2 **HCC in a chronic hepatitis C carrier. (a) Arterial phase helical CT shows a multinodular mosaic pattern with a central necrotic scar. (b) Delayed phase helical CT shows an enhancing pseudocapsule (white arrow). (c) The cut surface of the gross specimen shows a similar multinodular mosaic pattern. Note the presence of the pseudocapsule (black arrows).**

63%, whereas the pseudocapsule is seen in 31% and the mosaic pattern in 46% of CT examinations[16,18]. The diagnosis of HCC is raised when these imaging features are seen in hypervascular lesions.

Imaging diagnosis of hepatoma

It is tempting to make a non-invasive imaging-based diagnosis of HCC, especially in the cirrhotic patient, as liver biopsies have attendant risks of hemorrhage and seeding (3%)[19].

The EASL has proposed a set of non-invasive criteria for HCC in cirrhotic patients[14]. The diagnosis is established if two imaging modalities (US, CT, magnetic resonance imaging (MRI)) show a coincidental nodule with arterial hypervascularization regardless of AFP levels, or if a single modality shows a lesion when the AFP levels are more than 400 ng/ml. Histologic diagnosis is required if the patient is non-cirrhotic or if the lesions are smaller than 2 cm.

It is important to recognize the limitations of the presumptive diagnosis of HCC made by imaging and AFP. The imaging characteristics of HCC are not pathognomonic. Differential diagnosis of hypervascular lesions includes hypervascular metastases, adenoma, FNH, angiomyolipomas and Type 1 hemangioma[7]. Small enhancing nodules in the hepatic arterial phase, even if they appear round or oval, may represent arterioportal shunts and pseudolesions[20–24]. The signal characteristics of HCC on MRI show considerable overlap with dysplastic nodules and other lesions[25]. Lipiodol uptake is also not pathognomonic as dense homogenous uptake can be seen in focal nodular hyperplasia (FNH) and patchy uptake in hemangioma, metastases, and FNH[26]. AFP can be elevated in chronic hepatitis, fulminant hepatitis, cirrhosis and testicular tumor[19,27,28].

Hence if a lesion is operable for cure, the procedure establishing the diagnosis should be the curative liver resection[14,19].

Assessment of disease extent

Tumor node metastasis (TNM) staging is generally considered important in classifying tumors into prognostic groups[29]. However, in HCC, patient survival is also dependent on the functional reserves of the liver, which is often cirrhotic. The Okuda classification takes into account both tumor burden and liver function (bilirubin, albumin, ascites)[30]. Although it identifies end-stage cases, it does not discriminate well between early and advanced cases. More recent proposals attempt to improve the prediction of outcomes of advanced cases but none are universally accepted[31].

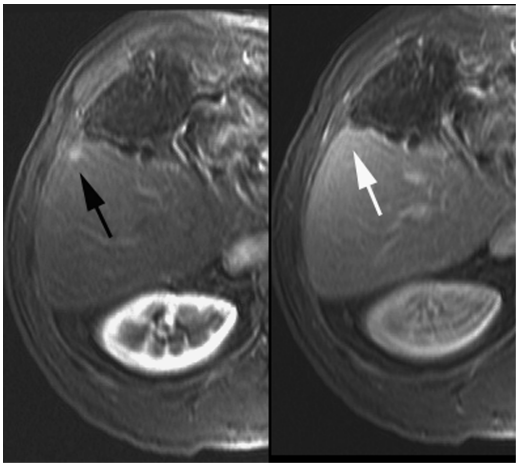


Figure 3 **Pseudolesion. This patient is a chronic hepatitis B carrier with previous resection of HCC. MRI was performed to evaluate rising AFP levels. A small enhancing lesion was noted in the arterial phase of the axial gradient-echo fat-suppressed T1-weighted series (black arrow). This was not seen in the portal venous phase (white arrow). Although the lesion was reported as indeterminate, surgery was performed in view of the elevated AFP. The lesion was not found during surgery. The affected area was nevertheless resected and histology showed benign liver tissue.**

The predominant role of imaging in staging HCC is to evaluate the involvement of the venous structures and to detect small additional lesions that may preclude surgery.

Identification of additional enhancing nodule in the hepatic arterial phase does not necessarily imply multiplicity. Pseudolesions and benign hypervascular lesions may mimic HCC[7,20–24]. There is also considerable overlap in the appearance of dysplastic and regenerating nodules, some of which may show hypervascularity in the arterial phase[32,33]. These difficulties and pitfalls are discussed in the following sections.

Hypervascular nodule—is it a real tumor?

Arterioportal shunts and pseudolesions are increasingly being recognized as mimics of HCC. More than a third of cirrhotics can demonstrate small enhancing nodules in the arterial phase which are the result of perfusion anomalies[22]. A large proportion of these pseudolesions are round or oval in shape[22,23] (Fig. 3). MR is a good modality to distinguish them from true lesions as the great majority of pseudolesions show no corresponding signal changes on T2-weighted scans[22,24]. This criterion is not absolute as small HCC less than 2 cm may not manifest signal changes on T2-weighted scans, and 8–26% of pseudolesions may show high signal on T2-weighted scans[24,34]. Some pseudolesions show a lack of uptake of superparamagnetic iron oxide (SPIO) and retention of Lipiodol[20,35]. In advanced cirrhosis requiring transplantation, two-thirds of non-arterial enhancing nodules more than 5 mm with no corresponding MR signal changes on other sequences are related to HCC[36].

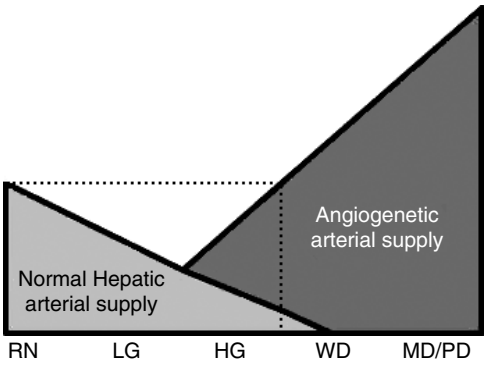
Despite imperfections, MR remains, in our opinion, the best modality at distinguishing pseudolesions from true lesions though overlap patterns exist. Lesions presumed to be pseudolesions should be followed up to confirm the diagnosis.

Hypervascular nodule and cirrhosis—is it HCC?

The presence of multiple nodules in the cirrhotic liver is a common imaging problem as the surgeon would often need to know the nature of each nodule before deciding on surgery.

Nodules in the cirrhotic liver may be regenerative, dysplastic or neoplastic. It is generally accepted that dysplastic nodules are premalignant for HCC. A theory of stepwise transformation of low-grade dysplastic nodules into high-grade dysplastic nodules and finally into HCC has been proposed and some supporting evidence is available[37–39].

Distinguishing the various nodules in a cirrhotic liver is difficult. One appreciates the problems better if one understands the blood supply of the various nodules. The blood supply of dysplastic nodules and HCC has been extensively investigated by CT hepatic arteriography (CTHA) and CT arterioportography (CTAP)[40]. As a nodule transforms, there is initially a decrease in hepatic arterial flow as the native hepatic arteries undergo degeneration. With increasing de-differentiation, there is a subsequent increase in angiogenesis and hepatic arterial supply. As such, there is theoretically a break-point where the decrease in normal supply is balanced by an increase in angiogenetic supply. This break-point occurs in high-grade dysplastic nodules or well-differentiated HCC (Fig. 4). As current imaging modalities rely on detection of increased hepatic arterial supply, it is not difficult to see how well-differentiated HCC or high-grade dysplastic nodules can be misdiagnosed.



Adapted from Hayashi, AJR AM J Roentgenol 1999; 172:969

Figure 4 **Schematic diagram illustrating the decrease in normal paired hepatic arterial supply and the increase in angiogenetic arterial supply as a nodule becomes more dysplastic and neoplastic. (Adapted from Hayashi M, Matsui O, Ueda K *et al.* Correlation between the blood supply and grade of malignancy of hepatocellular nodules associated with liver cirrhosis: evaluation by CT during intraarterial injection of contrast medium. AJR Am J Roentgenol 1999; 172: 969.) RN, regenerating nodule; LG, low-grade dysplastic nodule; HG, high-grade dysplastic nodule; WD, well-differentiated HCC; MD, moderately differentiated HCC; PD, poorly differentiated HCC. Note that there is a point in the continuum where the decrease in normal hepatic arterial supply is balanced by an increase in angiogenetic supply. This occurs in high-grade dysplastic nodules or well-differentiated HCC and explains the difficulty in diagnosis.**

Explant studies have shown the poor sensitivity of CT, MR and angiography for small (less than 2 cm) HCC[41–43]. The overall sensitivity of MR is 55% and specificity 86% in the explanted liver[43]. The sensitivity of detecting HCC smaller than 1 cm is only 33%. There is also considerable overlap in the imaging patterns between HCC and dysplastic nodules. Differentiation from HCC on the basis of MR signal is difficult although HCC generally have a high signal on T2-weighted scans[25,44].

Freeny found that 41 (67%) out of 61 hypervascular nodules on CT in patients undergoing transplantation were related to benign regenerating nodules; three (5%) were dysplastic nodules and only 17 (28%) were HCC[32]. Lim found that hepatic arterial supply was increased in 21% of low-grade dysplastic nodules and hypervascularity was absent in 38% of high-grade dysplastic nodules[33]. Matsui found that 6% of HCC do not show increased hepatic arterial supply[45].

Notwithstanding these difficulties, it is still generally accepted that a nodule demonstrating increased arterial flow in a cirrhotic liver should be treated as a HCC. Nodules that do not show early enhancement are probably benign but should be followed up.

Which imaging modality is best?

The ideal imaging modality must be sensitive in detecting hypervascular lesions. It must be able to distinguish between arterioportal shunts and true lesions. It should be able to identify the supporting imaging features of HCC such as pseudocapsule, internal septa and mosaic appearance.

Dynamic contrast-enhanced MR is the optimal modality for the above reasons. Dynamic contrast-enhanced MR is more sensitive than dynamic contrast-enhanced CT[42,46,47] (Fig. 5). A recent explant study showed that MR detected more small lesions between 1 and 2 cm compared with CT (84 vs. 47%)[36]. Studying the impact on management, MR indicated the correct decision in 90% compared with 77–80% for CT[36]. CT remains a useful modality in view of its availability.

Conflicting data exist regarding the relative sensitivity of CTHA/CTAP and MR[48–51]. However, due to the problem of pseudolesions with CTHA and CTAP, MR is generally preferred. Jang found that combined CTHA and CTAP detected 20 more hypervascular lesions than dynamic CT in 52 patients[52]. However, only two of the 20 lesions were HCC while the remainder were proven to represent pseudolesions.

MR is useful in identifying pseudolesions as a great majority of them do not show corresponding signal changes on the unenhanced T1- and T2-weighted scans. However, small HCC can behave like pseudolesions and follow-up scans are required to confirm the absence of growth[22].

Angiography has poor sensitivity even compared to CT[53]. The use of Lipiodol-CT is not recommended by the EASL due to its limited accuracy[14].

New contrast agents

New US microbubble contrast agents show promise in the evaluation of HCC. Although there are limited data on the use of microbubble contrast agents in hepatoma, contrast-enhanced US can detect small HCC occult on MR[54]. Microbubble-enhanced US correlates well with CT in the assessment of response to radiofrequency (RF) ablative therapy[55–57]. There is tremendous potential for the use of microbubble contrast in the identification of HCC during RF ablation. It can potentially increase the sensitivity and accuracy of intraoperative US examinations and help characterize the ‘new’ lesion found in the operating room.

Liver-specific (hepatocyte and reticuloendothelial) MR contrasts face problems of the well-differentiated HCC behaving like normal liver parenchyma and demonstrating contrast uptake. They currently have a problem-solving role in certain situations[8].

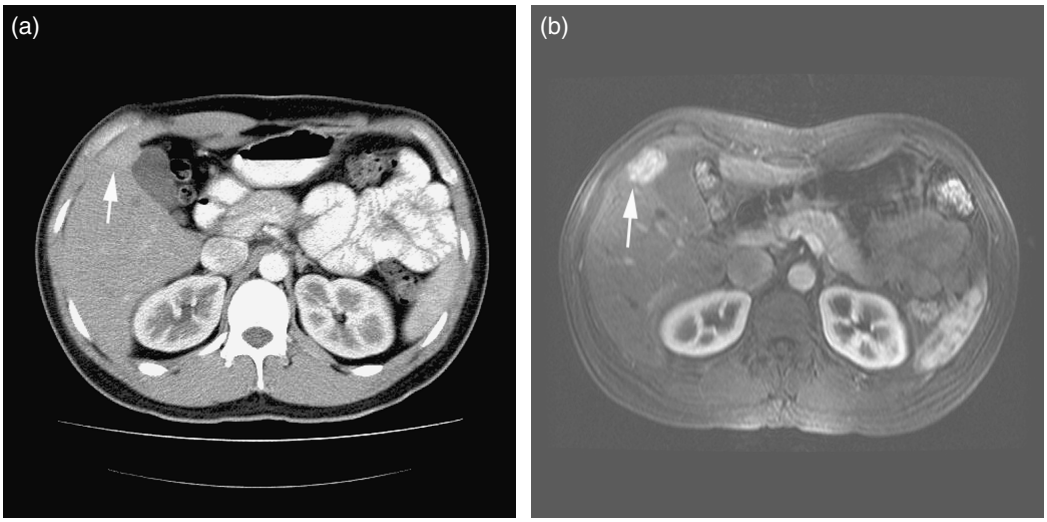


Figure 5 **HCC. (a) Arterial phase helical CT shows a slightly hyperdense lesion (arrow). (b) Arterial phase T1-weighted fat-suppressed 3D gradient-echo scan shows the hypervascularity (arrow) better than CT.**

Conclusion

Imaging diagnosis of HCC remains difficult. The diagnosis is suspected when a lesion demonstrates increased arterial flow, pseudocapsule, internal septa and a mosaic appearance. However, the radiologists should be aware of the pitfalls of pseudolesions and the overlap with dysplastic and regenerating nodules. MR appears to be a superior imaging modality although diagnosis of small (less than 2 cm) HCC remains difficult.

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