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# ROLE OF MDCT IN HEPATOCELLULAR CARCINOMA: A REVIEW ARTICLE

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## ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a major public health problem worldwide. Hepatocarcinogenesis is a complex multistep process at molecular, cellular, and histologic levels with key alterations that can be revealed by noninvasive imaging. MDCT as a fast, cheap and easily accessible imaging modality plays a major role in the clinical routine work-up of HCC. Technical advances in CT, such as multiplanar reformating(MPR) and volume perfusion CT are currently being explored for improving detection, characterization and staging of HCC with promising results. MDCT can provide a three-dimensional analysis of the liver with tumor and vessel characterization comparable to cross-sectional imaging so that this technique is gaining an increasing role in the peri-procedural imaging of HCC treated with interventional techniques. Therefore, imaging techniques play pivotal roles in the detection, characterization, staging, surveillance, and prognosis evaluation of HCC. While based on conclusive enhancement patterns comprising arterial phase hyperenhancement and portal venous and/or delayed phase wash-out, contrast enhanced dynamic computed tomography evaluation of tumor imaging characteristics, including nodule size, margin, number, vascular invasion, and growth patterns, allows preoperative prediction of tumor microvascular invasion and patient prognosis.

**Keywords:** hepatocellular carcinoma; multidetector computed tomography; multiplanar reformation; dual-energy computed tomography; volume perfusion computed tomography; contrast media; hepatocyte specific contrast media

## INTRODUCTION

Hepatocellular carcinoma (HCC) is an epithelial tumor originating in the liver and composed of cells with characteristics similar to those of normal hepatocytes [1]. It is the fifth most common tumor in the world, and its incidence is increasing, especially in Western nations [2]. Cirrhosis is the most important clinical risk factor for HCC, with approximately 80% of cases of HCC developing in patients with a cirrhotic liver [3]. In such patients, the annual incidence of HCC ranges from 2% to 8% [4, 5]. The exact incidence depends on the cause of cirrhosis (highest incidence in those infected with hepatitis C virus or hepatitis B virus), severity of cirrhosis (highest incidence in those with decompensated cirrhosis), geographic region (higher in Japan than in Europe or United States), and sex (higher in men than women). The risk is greater in individuals with multiple risk factors as well as in those coinfected with human immunodeficiency virus. Patients without cirrhosis also may develop HCC, especially those with long-standing chronic liver inflammation due to hepatitis B virus or hepatitis C virus infection [6] or nonalcoholic steatohepatitis [7], but at a much lower rate than those with cirrhosis. Other risk factors for HCC include heavy alcohol consumption, tobacco smoking [8], obesity, diabetes, hereditary hemochromatosis, high dietary consumption of aflatoxins, and family history of HCC. Importantly, cirrhosis and chronic hepatitis now are recognized as risk factors for intrahepatic cholangiocarcinoma (ICC) as well as HCC [9]; thus, many patients at risk for HCC may develop ICC instead. The prognosis of HCC depends largely on the stage at which the tumor is detected. Patients who present with symptoms generally have a dismal prognosis, as HCC usually does not produce symptoms beyond those of the underlying liver disease until it has become incurable; in such patients, median survival is less than 1 year and the 5-year survival is less than 10% [10]. By comparison, patients in whom HCC is detected at an early stage may benefit from life-prolonging, potentially curative treatments. The detection of HCC early in its development, therefore, is critical to improve the survival of affected patients. To this end, scientific societies have released clinical management guidelines that advocate surveillance of patients at risk due to cirrhosis or chronic viral hepatitis [4, 11, 12]. While the surveillance strategies incorporated by the various guidelines differ, all current guidelines recommend ultrasonography (US) as the primary imaging test for surveillance, and two guidelines advocate the ancillary use of serum biomarkers [4, 13]. In general, neither computed tomography (CT) nor magnetic resonance (MR) imaging are advocated for surveillance, although three guidelines permit these modalities for surveillance of patients in whom US is limited by obesity or other factors [4, 12, 13] and for those at very high risk for HCC development [4]. Once a surveillance test is positive (ie, an abnormality is detected that may represent HCC), a more definitive imaging examination is recommended for noninvasive diagnosis and staging of HCC. Currently, all guidelines endorse multiphasic CT and MR imaging with extracellular agents as first-line modalities for this purpose, although guidelines in Japan also advocate MR imaging with gadoxetate disodium (a hepatobiliary agent) as a second-line modality. In this review, we discuss about the present scenario regarding the imaging-based diagnosis and staging of HCC, focusing on MDCT imaging, as it is the most commonly used modality for these purposes. In this review we are discussing about the key concepts of HCC development, growth, and spread, emphasizing those features with imaging correlates and hence most relevant to radiologists; MDCT

imaging technique; and the imaging appearance of precursor nodules that eventually may transform into overt HCC. We are also discussing about the diagnosis and staging of HCC with MDCT imaging. Hepatocarcinogenesis, the gradual transformation of nonmalignant liver cells into HCC, is a complex, multistep process characterized at the molecular and cellular level by the progressive accumulation of epigenetic and genetic alterations [14] and at the histologic level by the emergence and progression of successively more advanced precancerous, early cancerous, and overtly malignantly lesions [15, 16].

## Hepatocarcinogenesis:

## Molecular and Cellular Mechanisms:

The molecular and cellular mechanisms underlying the transformation of initially onmalignant cells into HCC in chronic liver disease are not yet fully elucidated [17]. Growing evidence suggests that chronic inflammation plays a pivotal role by causing repeated cycles of cell injury, death, and regeneration–an environment that promotes aberrant cell signaling, epigenetic changes, mutational events, and accumulation of genetic damage [17-19]. These molecular alterations begin during a prolonged preneoplastic phase, years or decades before cirrhosis is established, and progress in parallel with the evolution of fibrosis and cirrhosis [20, 21]. During this phase, the alterations are mainly due to epigenetic mechanisms (eg, changes in gene expression) with few or no structural changes in the genes or chromosomes. The earliest molecular changes of hepatocarcinogenesis are morphologically silent [21-23]. Thus, the chronically diseased liver may contain scattered clonal populations of molecularly aberrant but phenotypically normal cells [21] that ultimately may progress to HCC. Subsequently, a neoplastic phase ensues in which structural alterations (eg, point mutations, allelic deletions, chromosomal gains and transpositions) in these aberrant cells escalate. During this phase, affected cells acquire progressively atypical phenotypic features and evolve through cellular intermediates to frank malignancy [19]. The genomic changes underlying hepatocarcinogenesis are heterogeneous, and diverse combinations of aberrant genes and regulatory pathways may be involved [1, 7, 18, 24]. Several molecular variants of HCC may be produced–potentially with different growth properties and clinical course–between patients, between different tumors in the same liver, and within different regions in the same tumor [19, 24]. Although most HCCs develop in cirrhotic livers, cirrhosis probably not a premalignant condition but rather a parallel process that develops over time in response to the same insults that promote hepatocarcinogenesis . The development of HCC usually is slower than that of cirrhosis; hence, most HCCs emerge after cirrhosis has been established.The cell of origin of HCC is controversial. Historically, it was assumed that most HCCs arose from dedifferentiation of mature hepatocytes. Emerging data suggest that HCCs also may develop from intrahepatic stem cells. These stem cells reside in niches within the canals of Hering and, according to new models of liver carcinogenesis, can be activated to differentiate into hepatocytes or cholangiocytes while undergoing oncogenic stimulation in the context of chronic liver injury [25]. The resulting tumors usually have predominantly hepatocellular (ie, HCC) or cholangiocellular (ie, ICC) phenotypic features, respectively, although some tumors may arise with combined or mixed features. If correct, these new models help to explain why patients with cirrhosis are at risk for developing ICCs and combined tumors in addition to HCCs.

## Hepatocarcinogenesis:

## Pathologic Changes:

Pathologically, multistep hepatocarcinogenesis is characterized by progressive dedifferentiation of phenotypically abnormal nodular lesions [15, 16]. The evolution is driven by the repeated development and expansion of successively less differentiated clonal populations, often manifesting as subnodules within parent nodules [26]. Over time, the less differentiated populations grow and completely replace the more differentiated surrounding tissues. Repeated cycles of clonal development and expansion eventually produce lesions with malignant phenotype. The process represents a biologic continuum but is arbitrarily ivided into discrete steps for simplicity, clinical utility, and investigation [27]. Importantly, the process may occur simultaneously at different rates in different parts of the liver (multicentric hepatocarcinogenesis). It should be emphasized that although most HCCs probably evolve from histologically abnormal precursor lesions, it is possible that many HCCs, especially those arising in noncirrhotic livers, may develop to transformed malignant cells without transitioning through histologically definable intermediate steps. The development of HCC without identifiable histologic precursors is termed "de novo hepatocarcinogenesis" [28].

**Cirrhotic nodules:** Cirrhotic nodules, also known as cirrhosis-associated regenerative nodules, are innumerable well-defined rounded regions of the cirrhotic arenchyma surrounded by scar tissue and typically measuring 1–15 mm in diameter. Cirrhotic nodules larger than 1 cm are called "large cirrhotic nodules" or "large regenerative nodules." Grossly and microscopically, cirrhotic nodules are indistinguishable from other cirrhotic nodules–in other words, all cirrhotic nodules in a given liver resemble each other and no cirrhotic nodule stands out as being distinctive from the others. Cirrhotic nodules lack clonal features histologically, and the cells are phenotypically normal [29]. For these reasons, cirrhotic nodules usually are considered "benign." The "benignity" of cirrhotic nodules is not unqualified, however. Based on molecular analyses, many cirrhotic nodules are clonal expansions of genomically aberrant cells [23], and he patocytes within cirrhotic nodules may develop dysplastic features and thus give rise to dysplastic foci and nodules. As discussed below, most cirrhotic nodules are not discernible as individual lesions at in vivo imaging.

**Dysplastic foci:** Dysplastic foci are microscopic lesions, arbitrarily less than 1 mm in diameter, composed of hepatocytes ith precancerous features such as small cell change arising within cirrhotic nodules or, if the liver is noncirrhotic, ithin single lobules [24]. These lesions are identified incidentally at histologic evaluation and not detectable by means of in vivo imaging. As it is not possible to detect or follow them in vivo, their natural history is poorly under stood. It is presumed that dysplasticfoci may expand to become dysplastic nodules.

**Dysplastic nodules:** Dysplastic nodules are nodular lesions, usually 1–1.5 cm in diameter, that differ in both macroscopic (size, color, or consistency) and microscopic appearance from background parenchyma. They are observed in up to 25% of cirrhotic livers but occasionally are detected in noncirrhotic livers and often are multiple. Dysplastic nodules are classified as low grade or high grade, depending on the presence of cytologic and architectural atypia [30]. histologically, low-grade dysplastic nodules resemble cirrhotic nodules. The hepatocytes show no cytologic atypia [30], and neither expansile subnodules nor architectural alterations

beyond those of cirrhotic nodules are observed [30, 31]. Findings, that if present distinguish low-grade dysplastic nodules from cirrhotic nodules include unpaired arteries and clone like populations (aggregates of cells with greater copper, iron, or fat accumulation than background liver) [16, 30]. High grade dysplastic nodules resemble well differentiated HCCs. The cells show cellular atypia, although the atypia is insufficient to establish a diagnosis of HCC, and may exhibit clone like features. Architectural alterations, including arrangement of hepatocytes in thin trabeculae and pseudoglands, may be present. Expansile subnodules with varying degrees of atypia may be observed. Clinically, low-grade dysplastic nodules are considered preneoplastic lesions with slightly elevated risk of malignant transformation, while high-grade dysplastic nodules are considered advanced precursors of HCC with high risk of transformation [16, 32]. Some high-grade dysplastic nodules contain one or more subnodules of well-differentiated or moderately differentiated HCC ("nodule-in-nodule" configuration); these are appropriately categorized as "HCC arising in high-grade dysplastic nodule". As discussed below, MDCT imaging has limited ability to identify and characterize dysplastic nodules.

## Early HCCs:

Early HCCs are an incipient stage of HCC development, analogous to "carcinoma in situ" or "microinvasive carcinoma" of other organs [33]. Unlike overt progressed HCC, which displaces or destroys the liver parenchyma (see below), early HCCs grow by gradually replacing the parenchyma; as the cells spread, they surround neighboring portal tracts and central veins but do not displace or completely destroy these structures. Early HCCs typically measure 1–1.5 cm in diameter and rarely exceed 2 cm. Macroscopically most early HCCs are vaguely nodular with indistinct margins and without a tumor capsule. Due to their small size and macroscopic appearance, these lesions frequently are termed "vaguely nodular small HCCs" or "small HCCs with indistinct margins." [29]. The lesions are indistinguishable from high-grade dysplastic nodule at gross pathologic examination. Histologically, early HCCs consist of small, well-differentiated neoplastic cells arranged in irregular but thin trabeculae or pseudoglands. Thus the microscopic appearance closely resembles that of high-grade dysplastic nodules. The key distinguishing feature, present in early HCCs but not in high-grade dysplastic nodule, is stromal invasion, defined as infiltration of tumor cells into the fibrous tissue surrounding portal tracts retained within the nodule or into the stromal fibrous tissue surrounding the nodule. While stromal invasion is characteristic, vascular invasion is not observed [34], and intrahepatic metastasis is exceedingly rare. Early HCCs are considered precursors of progressed HCCs, although the rate at which they transform to progressed HCC has not been defined [35]. Moreover, some progressed HCCs probably do not develop from early HCCs but rather arise as expansile subnodules within highgrade dysplastic nodules without transitioning through a vaguely nodular morphology. As will be discussed further in part 2 of this review, conventional CT and MR imaging have limited sensitivity for the detection of early HCCs, but hepatobiliary phase MR imaging shows promise for this purpose.

## Late HCCs:

Late HCCs are overtly malignant lesions with the ability to invade vessels and metastasize. Macroscopic and histologic features are variable, depending in part on lesion size. rogressed HCCs smaller than 2 cm are distinctly nodular with well-defined margins; synonymous terms include “small and progressed HCCs” and “small distinctly nodular HCCs.” Unlike early HCCs, small and progressed HCCs grow by expanding into and compressing the adjacent parenchyma. Characteristically, they are surrounded by a tumor capsule and contain internal fibrous septa. Histologically, about 80% of small and progressed HCCs are moderately differentiated; the remaining 20% consist of both well-differentiated and moderately differentiated components. Architectural abnormalities include thickened plates more than three cells wide and arrangement of hepatocytes in trabecular/platelike, pseudoglandular/acinar, or solid/compact patterns. A significant proportion of small and progressed HCCs are associated with vascular invasion and intrahepatic metastasis. HCCs exceeding 2 cm in diameter are known as “large HCCs.” Compared with small and progressed HCCs, large HCCs tend to have higher histologic grade, more aggressive biologic behavior, and higher frequency of vascular invasion and metastasis. For these reasons, it is clinically important to develop imaging techniques that can be used to accurately diagnose small HCCs prior to their growth beyond 2 cm. Macroscopically, most large HCCs are expansile tumors with nodular morphology and surrounded by tumor capsules. Mosaic architecture is characteristic, defined by the presence of multiple internal tumor nodules separated by fibrous septations and areas of hemorrhage, necrosis, and occasionally fatty metamorphosis [36]. Histologically, the internal tumor nodules may differ in grade, microscopic architectural pattern, and cytologic type. Molecularly, they may differ in epigenetic and genetic abnormalities. At least some of these nodules appear to arise through clonal divergence from common precursor clonal populations [37, 38]. About 5% of large HCCs have an infiltrative rather than an expansile growth pattern; these cancers usually are composed of poorly differentiated or undifferentiated cancer cells that spread into the surrounding sinusoids and cell plates, causing the tumor boundary to be ill defined.

## Multifocal HCC:

In more than one-third of patients, HCC is multifocal [39], defined by the presence of tumor nodules unmistakably separated by intervening non-neoplastic parenchyma. Multifocality are due to synchronous development of multiple, independent liver tumors (multicentric hepatocarcinogenesis) or intrahepatic metastases from a primary tumor. In the former case, the tumors may vary in histologic grade and other features; in the latter case, all the tumors are progressed lesions with advanced tumor grade. The prognosis of patients with multifocal HCC due to intrahepatic metastasis tends to be worse than in those with multicentric development of independent tumors [40]. Patients with HCC also are at high risk for future development of new tumors. Due to the high frequency with which multiple tumors may develop, patients with HCC sometimes cannot be cured by means of surgical resection or ablation; as long as the cancer has not spread outside the liver, hepatic transplantation may provide more prolonged survival.

## Spread of HCC:

## Intrahepatic Metastasis:

Although progressed HCCs may spread contiguously into the surrounding liver by expansile or infiltrative growth, the most important mechanism of spread is intrahepatic metastasis. These metastases develop in progressed HCC (but rarely if ever in early HCC) when malignant cells enter portal venules draining the primary tumor and spread into the surrounding parenchyma. (As mentioned earlier, the venous drainage evolves during hepatocarcinogenesis from hepatic venules to portal venules; the portal venules are thought to be the conduits by which progressed HCC metastasizes). The resulting metastases usually manifest as small "satellites" within the venous drainage area around the primary tumor [41]. Intrahepatic metastases also may form outside the drainage area, including in other segments or in thec ontralateral lobe. Some of these remote intrahepatic metastases may arise from tumor cells that entered thes ystemic circulation and then returned to the liver [42]. Rarely, widespread intrahepatic metastases cause the liver to be diffusely studded with minute, uniformly sized, poorly differentiated tumor nodules that at gross pathologic examination may mimic the appearance of cirrhotic nodules ("diffuse" or "cirrhotomimetic" HCC) [43]. Despite the tendency of HCCs to invade vessels and metastasize within the liver, extrahepatic metastases (lungs, lymph nodes, bones, adrenal glands) are late manifestations [10].

## Vascular Invasion:

Vascular invasion, the entrance of tumor cells into the lumen of vessels, is a characteristic feature of progressed HCC [44]. Such invasion distinguishes HCC from secondary liver cancers, which rarely invade intrahepatic vessels. Portal veins are invaded more commonly than hepatic veins; hepatic arteries are not invaded [44]. Vascular invasion is classified as microvascular (visible only at microscopy) or macroscopic (visible at gross pathologic examination). Both types of vascular invasion indicate a poor prognosis, as they provide the route by which HCC cells access the circulation to metastasize through the liver or systemically. Thus, HCCs with vascular invasion frequently are multifocal and have higher recurrence rates after resection, ablation, and transplantation [45]. Factors associated with vascular invasion include large tumor size and advanced histologic grade. The risk of recurrence is particularly high for patients with macrovascular invasion; for this reason, macrovascular invasion is regarded as a contraindication for surgical resection or liver transplantation.

## Biliary Invasion:

Bile duct invasion is uncommon clinically but reported in 5%–10% of autopsy series [37, 46]. Most cases are associated with infiltrative HCCs or HCCs with macrovascular invasion.

## Tumor Capsule Invasion:

HCC cells that elaborate metalloproteinases may infiltrate into and through the tumor capsule into the surrounding parenchyma [47]. Such infiltration increases the risk of vascular invasion and intrahepatic metastasis, and so is associated with poorer prognosis. MDCT imaging Technique, three enhanced phases

typically are acquired: late hepatic arterial, portal venous, and delayed phase. The late hepatic arterial phase is characterized by full enhancement of the hepatic artery and its branches as well as enhancement of the portal vein; the hepatic veins are not yet enhanced by antegrade flow [48]. This phase coincides with peak arterial perfusion and enhancement of liver tumors, and it is critical for detection and characterization of hypervascular HCC [49] (Fig 1). The early hepatic arterial phase, in which the hepatic artery is enhanced but the portal vein is not, is less effective, as tumor hypervascularity may be subtle or missed altogether. Most centers therefore omit the early hepatic arterial phase. Contrast agent bolus tracking or use of a test bolus is recommended for late hepatic arterial timing [50], since fixed delay is not reliable for this purpose. Another approach for achieving optimal timing is to obtain multiple high-temporal- resolution arterial-phase acquisitions, thereby ensuring that at least some images are captured during peak arterial perfusion and enhancement of the tumor. The portal venous phase coincides with peak parenchymal enhancement, is characterized by enhancement of hepatic veins as well as portal veins, and is acquired at around 60–80 seconds after the start of contrast agent injection (Fig 1). The delayed phase is acquired at 3–5 minutes [51] (Fig 1). As discussed further in part II, these latter phases are critical for characterizing key imaging features of HCC such as washout appearance and capsule appearance [52] (Fig 1), and they help to differentiate small HCCs from small ICCs, which typically show prolonged central enhancement (94). For the above purposes, the delayed phase may be superior to the portal venous phase [53] (Fig 1). The portal venous and delayed phases also may be useful for measuring nodule diameter, depicting hypovascular nodules including early HCCs, and identifying vascular thrombosis. To reduce radiation dose, some centers skip the delayed phase at CT, but this practice is difficult to recommend because important diagnostic information may be lost. In theory, precontrast CT also might be helpful in patients with iron-rich nodules to detect hyperattenuation before contrast agent administration, thus avoiding misinterpretation of arterial-phase hyperenhancement, but there is little published evidence to our knowledge to support this benefit. Thus, except in patients previously treated with locoregional embolic or ablative therapies, precontrast CT adds little diagnostic value [54] and, to reduce radiation dose, usually may be omitted from routine multiphasic examinations without loss of significant diagnostic information. In the future, dual-energy CT may be of value by permitting the generation of virtual unenhanced images and/ or iodine maps that depict the iodine concentration distribution in tumor and background liver.

## Characterization:

## Cirrhotic Nodules:

Although cirrhotic nodules are innumerable in cirrhosis, most cirrhotic nodules are imperceptible or only barely perceptible at CT imaging. Relative to background parenchyma, these nodules usually are isoattenuating at unenhanced CT. After extracellular contrast agent injection, most cirrhotic nodules enhance to the same degree as the adjacent liver or show slightly less enhancement, in which case they may be visible in the portal or delayed phases at CT imaging as mildly hypoenhanced nodules relative to enhancing fibrosis. Cirrhotic nodules that are hyperenhanced in the arterial phase have been reported, although the mechanism is unclear because cirrhotic nodules do not show histologic evidence of neo-arterialization [55]. Since OATP

expression is preserved, cirrhotic nodules typically have similar signal intensity to surrounding liver parenchyma in the hepatobiliary phase after hepatobiliary contrast agent administration or they may appear subtly hyperintense relative to cirrhotic scars, which do not contain hepatocytes and hence do not uptake the agents. Some cirrhotic nodules may be markedly more hyperintense in the hepatobiliary phase than background nodules, presumably because they have sufficient hepatocellular function to take up the agent but not to excrete it [56].

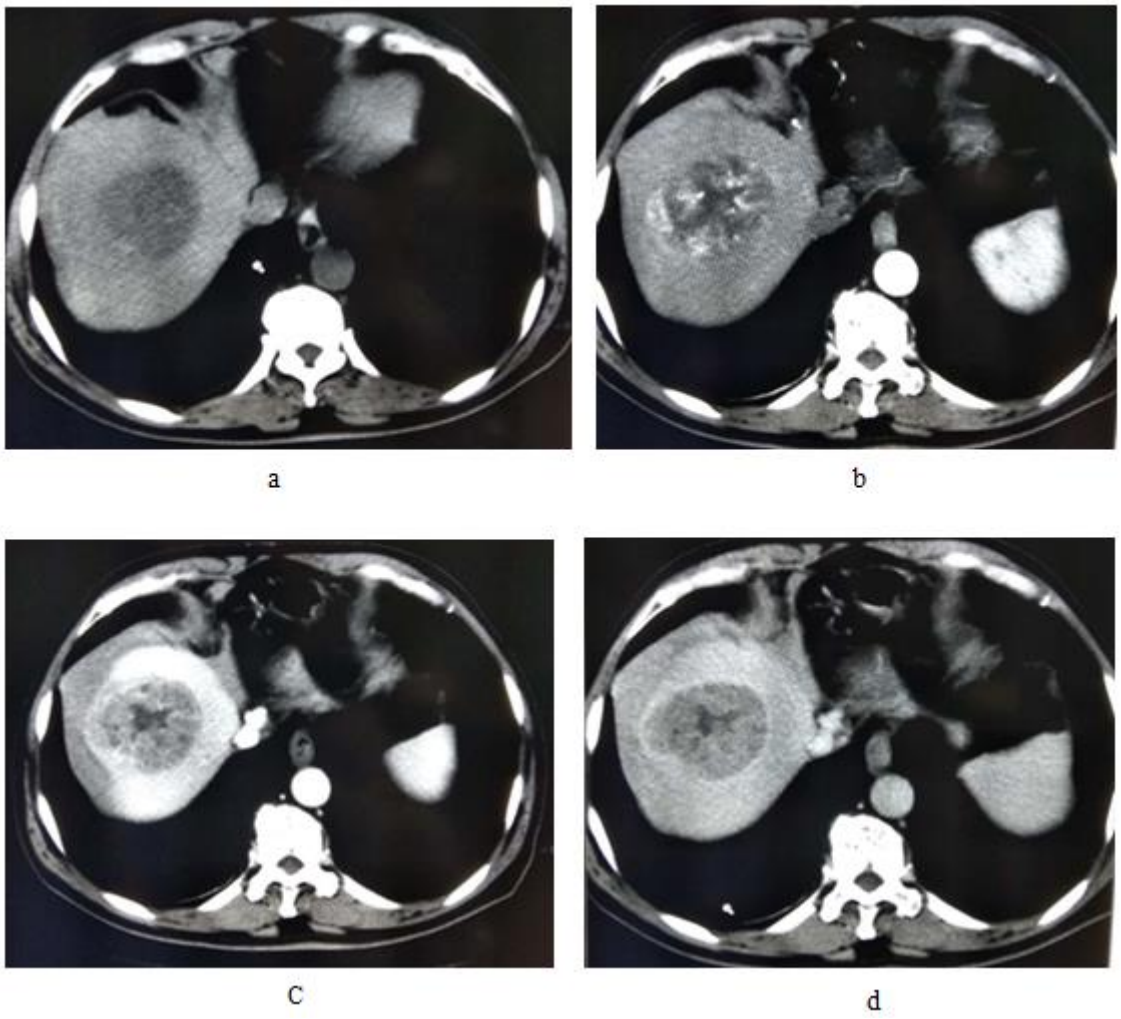


**Figure 1:** Images in a 63-years-old male with HCC with cirrhosis: multiphasic CT technique. (a) There is hypodensed lesion shown on precontrast CT image. (b) Early arterial phage image shows heterogeneously enhanced mass but not adequately enhancing and generally not useful in detecting HCC (c) Late hepatic arterial phase image shows heterogeneously hyperenhancing mass. Notice enhancement of hepatic artery and portal vein branches in late hepatic arterial phase. Hepatic veins are not enhanced. (d) Relative to liver, mass de-enhances or gets washed out on (d) portal venous phase image. Mass has capsule appearance in venous phases. Notice that hepatic veins are enhanced in portal venous and delayed phases.

In summary, while most cirrhotic nodules are imperceptible or only barely perceptible at CT imaging, some cirrhotic nodules may differ in appearance from background nodules due to unusual imaging features such mild portal venous or delayed phase hypoenhancement, or hepatobiliary phase hyperintensity. Such cirrhotic nodules cannot be distinguished from low- or high-grade dysplastic nodules at imaging.

## Dysplastic Nodules:

Most dysplastic nodules are isoattenuating or hypoattenuating in the arterial, portal, and delayed phases at CT. Large dysplastic nodules may appear hyperattenuating relative to liver at unenhanced CT and become isoattenuating after contrast material administration [57]. Some dysplastic nodules may contain intracellular iron in high concentrations. Such iron-rich or siderotic nodules appear slightly hyperattenuating at unenhanced CT. Some dysplastic nodules, especially high-grade dysplastic nodules, may contain intracellular fat in higher concentration than background liver. Such dysplastic nodules appear hypodense on unenhanced CT. Intralesional steatosis is more frequent in early HCC than in dysplastic nodules and also may occur in progressed HCCs, however, the detection of intracellular lipid is not diagnostic of dysplastic nodule [58]. Low-grade dysplastic nodules and most high-grade dysplastic nodules have relatively preserved arterial blood supply and so usually are isoattenuating or isointense to liver in the late hepatic arterial phase at CT imaging. Some high-grade dysplastic nodules have elevated arterial supply due to neo-arterialization and enhance more than liver in the late hepatic arterial phase, potentially being mistaken for hypervascular, progressed HCC. Analysis of portal venous and delayed phase images is helpful for interpreting arterial-phase hyperenhanced nodules. Hypervascular high-grade dysplastic nodules rarely show washout or capsule appearance in the portal venous or delayed phases, while these features are characteristic of progressed HCC [59]. Thus, the combination of arterial phase hyperenhancement and either washout or capsule appearance is considered diagnostic of HCC. Cirrhosis-associated nodules without arterial-phase hyperenhancement include cirrhotic nodules, low-grade dysplastic nodules, high-grade dysplastic nodules, and early HCCs. CT and MR imaging with extracellular agents are unreliable in the differentiation of such nodules, as each nodule type may show isoenhancement or hypoenhancement in all postcontrast phases [59]. Hepatobiliary contrast agents show promise for differentiating early HCCs and premalignant nodules (high-grade dysplastic nodules) from lower-risk nodules (low-grade dysplastic nodules and cirrhotic nodules). Since OATP expression declines during hepatocarcinogenesis, hepatobiliary phase hypointensity is a strong predictor of premalignancy or malignancy, and its presence favors highgrade dysplastic nodule or early HCC over low-grade dysplastic nodule or cirrhotic nodule [60]. A potential pitfall is that iron-rich lowgrade dysplastic nodules may appear hypointense in the hepatobiliary phase. Thus, in nodules with imaging evidence of iron accumulation, hepatobiliary phase hypointensity is nonspecific.

## CONCLUSION

HCC is an increasingly common cause of cancer death in the world. Hepatocarcinogenesis is caused by the progressive accumulation of epigenetic and genetic alterations potentially involving many different genes and regulatory pathways. In the long run it develops as chronic liver disease. Most HCCs emerge after cirrhosis

has been established. Growing evidence suggests that many HCCs arise from hepatic stem cells, which in part may explain the predisposition of patients with cirrhosis and chronic hepatitis to develop tumors. Histologically, hepatocarcinogenesis is characterized by the repeated emergence and expansion of successively less differentiated precursor nodules. Key alterations during hepatocarcinogenesis include elevation of arterial flow, reduction in portal venous flow, and reduction in OATP expression. Changes in fat and iron content also may occur. Multiphasic CT imaging with extracellular agents permit diagnosis of HCC based mainly on assessment of vascularity. Contrast enhanced phases include the late arterial, portal venous, and delayed phases.

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