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A Short Review on Progressed Hepatocellular Carcinoma: Radiological Findings and Histopathological Diagnosis

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ABSTRACT
Background: Hepatocellular carcinoma (HCC) is, by far, the most common liver malignancy. The risk factors for the development of HCC are numerous with liver cirrhosis, chronic hepatitis B and C viral infections and alcohol abuse on top of the list. Several studies were devoted to evaluate the complex radiological appearance of HCC and its correlation with histopathologic grade/stage as well as possible mimickers of HCC, all of which have a significant impact on diagnosis and management of patients with HCC.
Objectives: Evaluation of the radiological findings of HCC and its correlation with histopathologic grade/stage as well as mimickers of HCC.
Methods: This is a review article of some of the existing literature regarding radiological findings and histopathologic diagnosis of progressed hepatocellular carcinoma.
Conclusion: Imaging findings of progressed HCCs are complex and different from the standard findings of well-differentiated HCCs. Evaluation of enhancement and washout patterns, as well as the possibility of the presence of microvascular invasion, should be undertaken by the reporting radiologist and delivered comprehensively to the treating multidisciplinary team for proper management.
Keywords: Radiology, HCC, CT, MRI, Liver.

1. INTRODUCTION

The prevalence of hepatocellular carcinoma (HCC) has been increasing worldwide, especially in North America and Europe during the last few decades [1, 2]. This tremendous increase in incidence can be attributed to multiple factors including the rising prevalence of hepatitis B and C viral infections, alcohol abuse and nonalcoholic fatty liver disease among others [1]. Liver cirrhosis of any etiology is considered one of the strongest risk factors for developing HCC. Also, HCC is the most common primary liver malignancy in cirrhotic and non-cirrhotic livers [3]. For all of the aforementioned facts, there has been extensive research and institutional reviews on surveillance, diagnosis, and management of HCC. In the presence of risk factors, the diagnosis of HCC relies solely on imaging findings alone, further emphasizing the importance of a clear, well-structured surveillance and diagnostic approach. In not a small group of patients, the diagnosis is often complex due to different histological stages/grades of the tumor. The radiologist should be aware of such radiological-histopathologic findings correlation in order to predict the tumor behavior and response to therapy as well as include/exclude the patient from the liver transplant list after discussion with the multi-disciplinary treating team.

2. LI-RADS FOR HCC DIAGNOSIS

Liver cirrhosis patients are at a significantly increased risk for the development of HCC, several worldwide scientific institutes have published recommendations regarding surveillance for adult patients with cirrhosis [4]. The imaging modality for surveillance of patients with cirrhosis is transabdominal ultrasound (US) and once a focal nodule is discovered in a patient with liver cirrhosis, further imaging workup with either contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) is usually recommended [4, 5]. Both modalities require the intravenous administration of contrast which might be contraindicated in patients with certain degrees of renal impairment or allergies.

Liver Reporting & Data System (LI-RADS) is applied only for patients with high risk for developing HCC including liver cirrhosis, hepatitis B viral infection and current or prior HCC. LI-RADS must not be applied to patients without risk factors, with vascular origin of cirrhosis or to patients who are under 18 years old. LI-RADS major criteria include central (non-rim) arterial phase hyperenhancement, central (nonperipheral) washout, enhancing capsule/pseudocapsule and threshold growth. It is recommended that threshold growth is to be evaluated on the same sequences between studies [5]. LI-RADS also describes ancillary features to help the radiologist in categorizing the lesion of interest and can sometimes be used to upgrade or downgrade the lesion. The ancillary features favoring malignancy, in general, are ultrasound visibility as a discrete nodule, corona enhancement, fat sparing in a solid mass, restricted diffusion, mild-moderate T2 hyperintensity, and hepatobiliary phase hypointensity [4]. While some

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ancillary features favoring HCC, in particular, are non-enhancing capsule, nodule-in-nodule appearance, mosaic architecture, fat in mass more than background liver and blood products in a mass (Figure 1). The LI-RADS ranges from LR-1, which is favoring benignity to LR-5 that is favoring malignancy. The major criteria often lead directly to the assignment of the LI-RADS score and ancillary features may be useful as a tie-breaker [4, 5].

3. PATHOLOGY OF PROGRESSED HCC

HCC gross pathology and morphologic studies have shown that many HCCs arise in indeterminate nodules, such as dysplastic nodules in cirrhotic livers. At the same time, the well-differentiated HCC (WD HH) can progress to a dedifferentiated HCC in a multiphase process [6]. The prognosis of multiple HCCs from intrahepatic metastasis is poorer with a more aggressive course than independent HCCs tumors that emerge more or less simultaneously [7]. A consensus for hepatocellular carcinoma from the world health organization (WHO) proposed that early HCC are usually WD HCCs, smaller in size (< 2 cm) with ill-defined margins and are vaguely nodular while progressed HCCs (PD HCC) are usually larger (> 2 cm), moderately differentiated (MD HCC) and distinctly nodular (Table 1) [6, 8]. PD HCC is usually classified into three macroscopic groups: massive, diffuse and nodular [6]. Massive HCC type is defined as a sizable lesion with ill-defined margins and it is usually seen in advanced stage [7]. There are three common histopathologic growth patterns, namely, trabecular, pseudo-glandular and compact [6, 7]. The described classic histopathologic features of HCC are that they are richly vascularized lesions showing prominent trabeculations (> 3 cells), prominent acinar morphology, various degrees of cellular atypia, high mitosis and vascular invasion. On the other hand, PD HCC demonstrates an infiltrative and insinuating histological growth pattern with the development of new arterial supply (neovascularization) as well as vascular invasion. Interestingly, this appearance is well appreciated in the nodular type of early as well as PD HCC [6, 7, 9].

4. IMAGING FINDINGS

a. POORLY DIFFERENTIATED HCC

The presence of atypical enhancement patterns in well-differentiated HCCs as well as poorly differentiated HCCs using CT, ultrasonography, and MRI, is not an unusual finding. **Asayama *et al*** [28] studied the appearance of 60 HCCs on the CT arterial phase and stated that the arterial supply was reduced in the advance HCC as it progressed from MD HCC to PD HCCs. Another study confirmed that the arterial enhancement usually increased from WD to MD HCCs, while there was a reduction of arterial enhancement as the lesion transformed from MD to PD HCCs. Interestingly, among the three types, PD HCCs were the commonest to show hypo-enhancement during the arterial phase. Intratumoral arterial growth was mostly seen in advanced HCCs, namely PD (65%) and MD HCCs (64%) (Fig 1). Tumor necrosis on CT was rarely seen WD HCCs where it was more commonly seen with advanced HCCs (MD and PD). This finding is consistent with the fact that WD HCCs are composed of well-organized hepatocytes and form trabeculae, cords, and nests, while PD HCCs have pleomorphic, anaplastic and giant cells with central necrosis due to poor vascularization [6] .

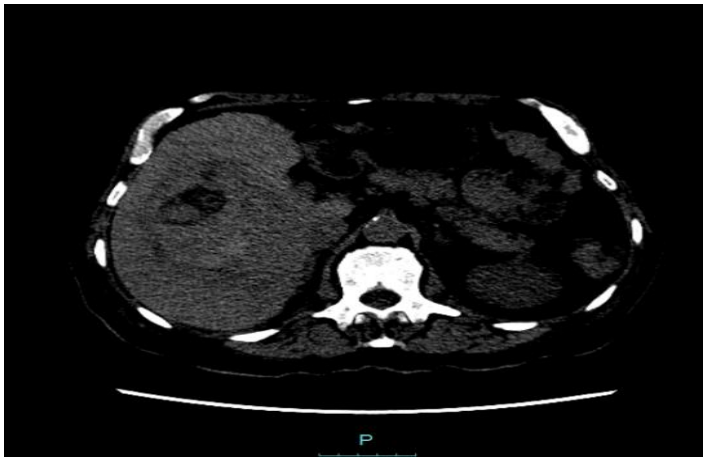

Figure 1 a

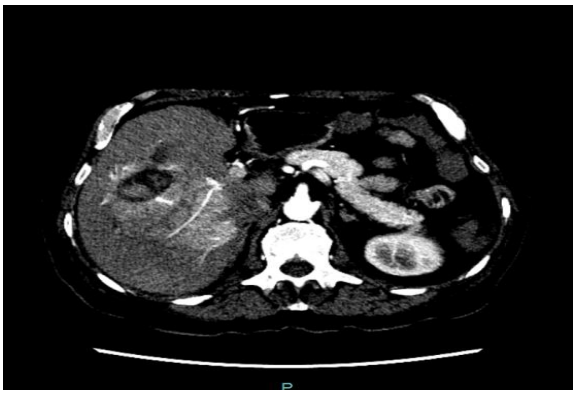

Figure 1b

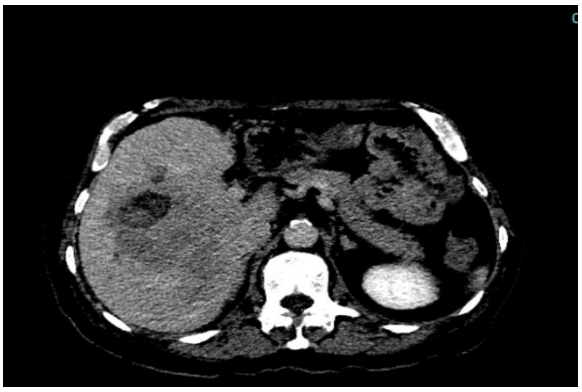

Figure 1c

Figure (1): Unenhanced (A), arterial (B) and delayed (C) images of CT scan of the abdomen showing a well-defined heterogenous large lesion noted in the segment 5/6 which shows diffuse arterial hyperenhancement and delayed washout. There is a hypodense lesion with the mass with fat attenuation and containing a solid enhancing nodule representing a nodule within nodule appearance

b. INFILTERATIVE HCC

HCC has three major growth types according to the Eggel classification: diffuse, nodular, and massive. The diffuse or infiltrative type is characterized by the spread of tumor micronodules throughout the liver or an anatomical lobe without a discrete nodule [10, 11]. Underlying liver cirrhosis was seen in most of the Infiltrative HCCs and several studies have referred to this type as cirrhotomimetic-type HCC [12]. The spread of HCC nodules throughout the liver is the typical pathologic macroscopic appearance of this type of HCC [10]. The radiological pattern is seen as a permeative ill-defined appearance at CT, MR and US imaging. Infiltrative HCC is usually associated with satellite lesions [10, 13]. Tumor invasion to the portal vein is a common finding in infiltrative HCC and hepatic venous thrombosis is less frequently reported (Figure 2) [14]. At contrast-enhanced cross-sectional imaging, infiltrative HCC has a vaguely ill-defined appearance and can be difficult to distinguish from underlying cirrhotic parenchyma because of, faint arterial enhancement, and the heterogeneous washout in venous phase which serves as an important sign of infiltrative HCC [10, 15]. **Kneuertz *et al.*** [13] Found that this washout phenomenon was seen in a large number of multifocal HCC (77.4%) but was seen in almost 50.8% of infiltrative HCCs. On MRI, the tumor is usually hypointense during the hepatobiliary phase after the injection of hepatobiliary specific contrast agents [10].

c. Microvascular invasion

Microvascular invasion (MVI) is a strong predictor for poorly differentiated tumors. As the tumor progresses from WD HCC to PD HCC, the tumor size increases and the tumor cells infiltrate the fibrous capsule and the prevalence of MVI increases [16-18].

Moribata *et al.* [19] studied the ultrasound findings for the correlation between B mode and tumor differentiation of small HCC. They stated that most of the small PD HCCs were visualized as a hypoechoic nodule with irregular or unclear margins.

A study by **Sugimoto *et al*.** [16] using contrast-enhanced US predicted PD HCC with possible MVI based on tumor angioarchitecture. They describe the deadwood pattern of HCCs for prediction of MVI which seen as intratumoral blood vessels that gradually tapered off or were suddenly interrupted. Contrast-enhanced CT is a commonly used modality for HCC diagnosis and used to assess tumor vascularity and morphology (Fig 3). **Asayama *et al.*** [28] found that HCC lesions arterial blood supply decreases in poorly differentiated HCCs compared to other HCCs. Irregular tumor margins in the delayed phase are an important predictor of MVI as stated by **Reginelli *et al.*** [20]. In their study, they found that irregular tumor margins and irregular peritumoral capsule are the most significant characteristics predicting MVI. A meta-analysis by **Hu *et al.*** [21] found that CT is superior to MRI in the evaluation of irregular tumor margins for predication of MVI. Other factors to predict PD lesion or MVI on CT are heterogeneous enhancement with hypovascular areas, fast contrast washout, complete peritumoral capsule, intra-tumoral and irregular tumor margin [16, 18, 22]. MRI performed using gadolinium-ethoxybenzyl diethylenetriamine penta-acetic acid is now commonly used for the diagnosis of HCC and have been used for predicting MVI on hepatobiliary phase. **Kim *et al.*** [22] concluded that peritumoral hypointensity on the hepatobiliary phase is a predictor for MVI. A study by **Lee *et al.*** [23] found that the combination of two or more of the following findings; irregular tumor margin, peritumoral hypointensity and arterial peritumoral enhancement are useful as biomarkers for predicting MVI [16]. Furthermore, to improve the sensitivity for predicting MVI, combined evaluation of the lesion using unenhanced MRI sequences including DWI and enhanced MRI are useful due to the high sensitivity of DWI [16, 24] .The radiological features related to poor prognosis summarized on table 1.

Table (1): Radiological findings related to worse prognosis

Radiological findings	Diagnostic value	Prediction for HCC differentiation	Poor prognosis
Tumor Size	+	-	+
Nodule within Nodule appearance	+	+	+
Corona enhancement	+	-	+
Irregular tumor margin	+	+	+
Multiple lesion	-	-	+

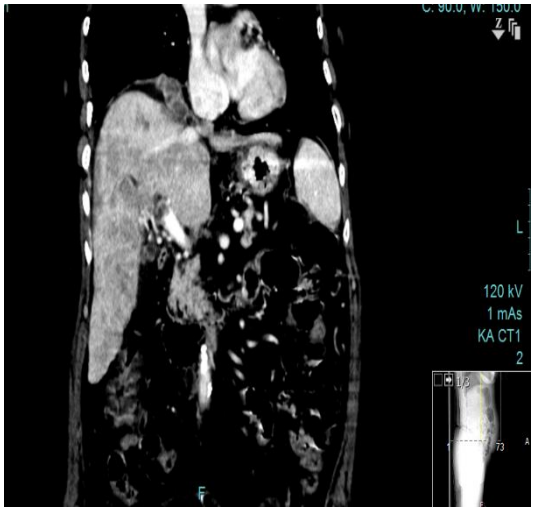

Figure 2b

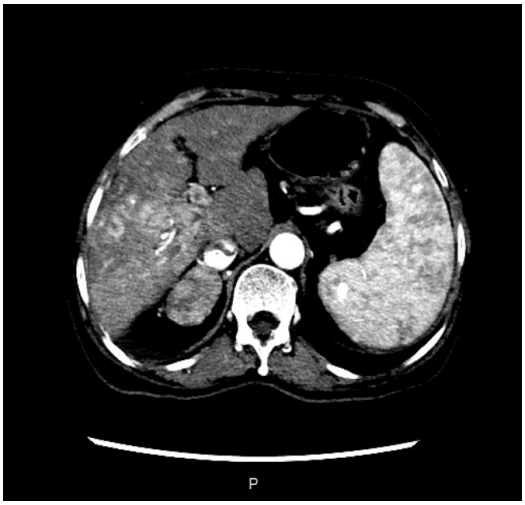

Figure 2a

Figure (2): Axial (A) and coronal (B) images of contrast enhanced CT scan of the abdomen during the arterial phase showing multiple irregular hypervascular lesions distributed throughout the right hepatic lobe which show intense arterial hyperenhacement consistant with known HCC. There is a right portal vein enhancing filling defect reaching to the division of the left and right portal veins indicating intravascular tumor extension.

5. MIMICKERS

Atypical imaging appearance of HCCs is not uncommon adding more diagnostic challenges for radiologists. It is critically important to distinguish these mimickers from HCC lesion [(25)].

Cholangiocarcinoma is a common mimicker of HCC especially the mass forming type and shares some risk factors with HCCs such as viral hepatitis and cirrhosis (Fig3)The key imaging feature to differentiate a large cholangiocarcinoma from HCC is the peripheral arterial enhancement and delay filling of the lesion (Figure 3). Another mimicker is the combined type cholangiocarcinoma with HCC which is an uncommon primary tumor, carries a poor prognosis and usually contraindicated for liver transplant. Typical imaging features for the combined type depend on the predominant histological element. Therefore, tumor markers such as Carbohydrate antigen 19-9 and alpha-fetoprotein levels are important to establish diagnosis [(24, 25)].

Some benign lesions may also mimic HCCs. Hepatic hemangioma is one of the mimickers especially the small lesion which does not show the typical imaging features of a hemangioma. However, HCC will show a washout instead of progressive filling expected in hemangiomas. Another benign mimicker is the hepatic adenoma which is composed of hepatocyte arranged in plat-like fashion with dilated sinusoids and usually seen in young women with a history of oral contraceptive pill use without risk factors for developing HCC [(25-27)].

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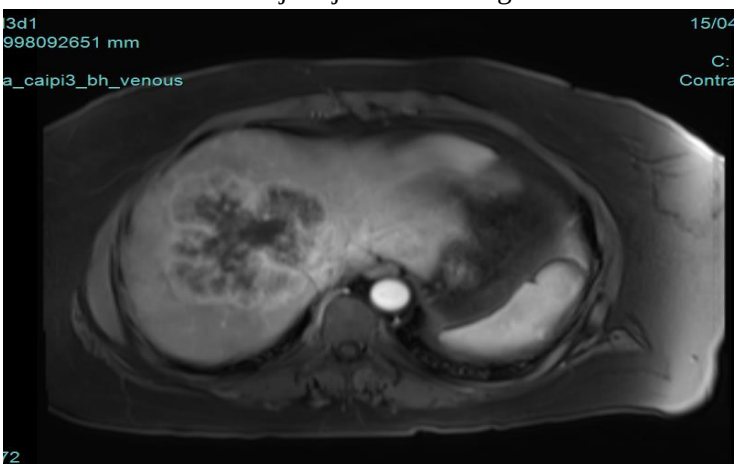

Figure 3a

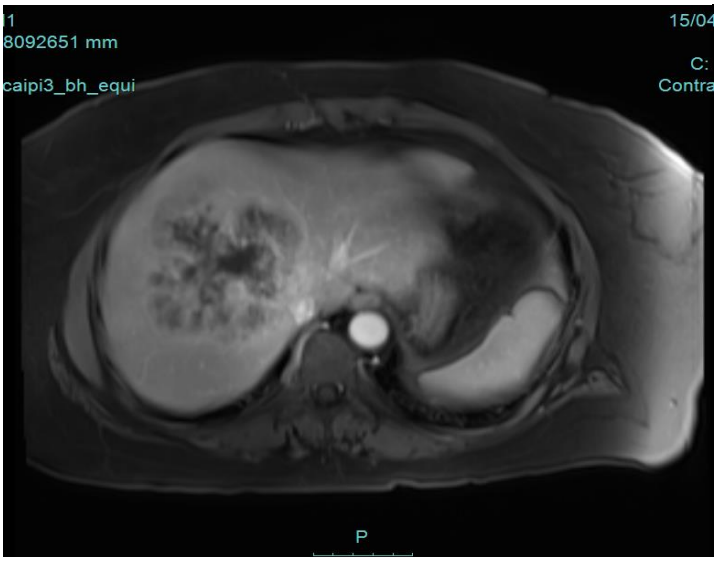

Figure 2b

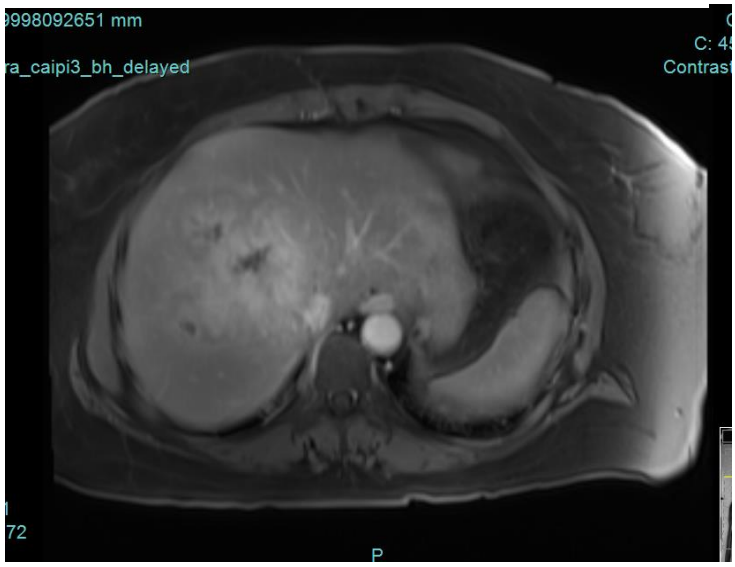

Figure 3c

Figure (3): Venous (A), equilibrium (B) and delayed (C) Gadolinium-enhanced MRI of the liver showing a well-defined heterogenous multilobulated mass in the segment 7/8.

The mass demonstrates early peripheral hyperenhancement with progressive central enhancement in the equilibrium and delayed phases consistent with biopsy proven cholangiocarcinoma. Also, central necrosis and peripheral delayed washout noted.

6. CONCLUSION

Hepatocellular carcinoma is the most common primary hepatic malignancy with several radiological and histopathologic appearances. Knowledge of the risk factors, pathogenesis, and histopathologic appearances is crucial for proper patient categorization and management.

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