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Capsular Enhancement in Hepato Cellular Carcinoma - A Short Review

Review Article

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Introduction

Hepatocellular Carcinoma (HCC) is the most common primary malignancy and the most common cause of cancer-related death among patients with chronic liver disease. Hepatitis B and C infections are recognised risk factors. Other risk factors are hepatic fibrosis due to metabolic diseases like hemochromatosis, Wilson's disease, biliary cirrhosis and aflatoxins etc. Every year approximately 350,000 new cases are diagnosed in the world [1,2]. It is more common in 60-70 yrs of age group with a male predominance. Serum alfa fetoprotein is a helpful laboratory test for initial screening. Several imaging modalities like USG, CT SCAN, MRI, PET CT have largely replaced biopsy for diagnosis. Dynamic multiphase CT and contrast MRI are the imaging modalities of choice. Functional imaging like perfusion, diffusion weighted images, elastography give additional information for characterisation, diagnosis, treatment and follow up. A recent AASLD statement recommended that tumors more than 1cms with typical enhancement pattern on dynamic CT need no biopsy [3]. Early diagnosis of HCC by imaging is desirable, as various treatment options like liver transplantation, segmental resection and local ablation therapy can be offered early leading to better outcome [4].

Imaging features

The HCC can be macroscopically classified into 3 main patterns. The most common is expansile single nodular, well defined, encapsulated with better prognosis, seen in 50% cases. Another variety is infiltrative lesions without capsule and frequently has vascular invasion. The third one is multifocal lesions in multiple liver segments [5]. Microscopically it ranges from well differentiated to undifferentiated. Radiologically it may present as massive focal mass/ multinodular or diffuse.

Diverse CT findings of HCC like mosaic pattern, venous invasion, tumor capsule, intra-tumoral abnormal vessels and arterioportal shunting have been reported [6]. However typical HCC shows arterial phase enhancement and wash out in portal venous and or in equilibrium phase in contrast enhanced CT and MRI (Figure 1). Capsular enhancement in portal or in equilibrium phase is an important diagnostic feature of HCC. A fibrous capsule frequently observed around the tumor during growth. Even according to LI-RADS, the major features of HCC are arterial phase enhancement, size of lesion, portal venous phase wash out, enhancing capsule in portal-venous phase/delayed /equilibrium phase and spread of tumor over a threshold [7].

The Capsule

A capsule is defined as a smooth continuous area along the periphery of the lesion that had different attenuation than surrounding liver as opposed to ring enhancement. On MDCT the capsule appears as curvilinear border surrounding at least half of the

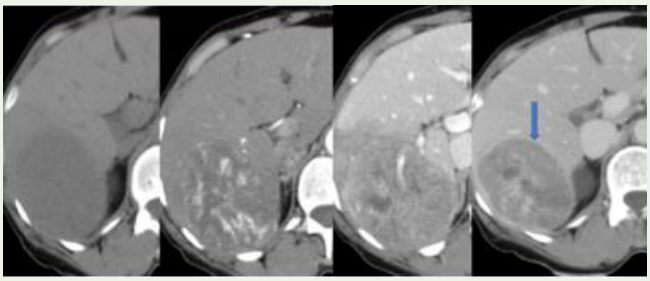

Figure 1: 44F, Neovascularity with aneurysmal dilatation in arterial phase and well-defined smooth capsule in equilibrium phase in moderately differentiated carcinoma.

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tumor. Capsule appearance is noted in 43 to 64% cases (Figure 2 and 3) [8,9]. This capsular appearance is seen in portal venous /equilibrium phase and appears as thick capsule. Arterial phase enhancement and capsular enhancement are major diagnostic criteria of HCC. Histologically fibrous capsule has inner layer of fibrous tissue and outer layer of portal venules and newly formed bile ducts. There are many hypotheses for fibrous capsule formation- one is because of passive thickening of liver stroma due to compression pressure of liver parenchyma; other it may be due to defence reaction of liver stroma to restrain mechanical injury caused by the tumor nodule [10]. This capsule represents a zone where the tumor communicates with adjacent parenchyma.

The capsule is formed by host of mesenchymal cells and not by HCC. Since the capsule formation is result from interactions between the tumor and host liver, it interferes with the growth and invasion of HCC [11]. This is supported by clinical evidence that prognosis of patient with HCC having capsule is better than those without capsule [12]. Majority of HCC in cirrhotic liver are well circumscribed and encapsulated whereas in non- cirrhotic liver are infiltrative. Fibrolamellar HCC show heterogenous enhancement in late arterial phase with evidence of non-enhancing central scar. It becomes isodense to rest of adjacent parenchyma in portal venous phase and wash out in equilibrium phase as seen in classic HCC in noncirrhotic liver. Capsular enhancement when present, it is seen in equilibrium phase and they have discontinuous capsule in 35% cases [13]. Development of HCC in cirrhotic liver is a multiphase process- starting from regenerative nodule to low grade dysplastic nodule to high grade dysplastic nodule with subsequent progression to HCC

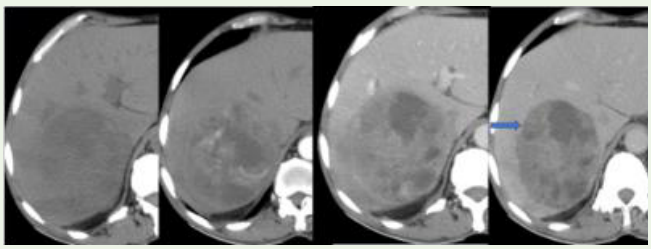

Figure 2: 63M, Arterial phase enhancement and wash out in PV and equilibrium phase with no capsular enhancement in well-differentiated carcinoma.

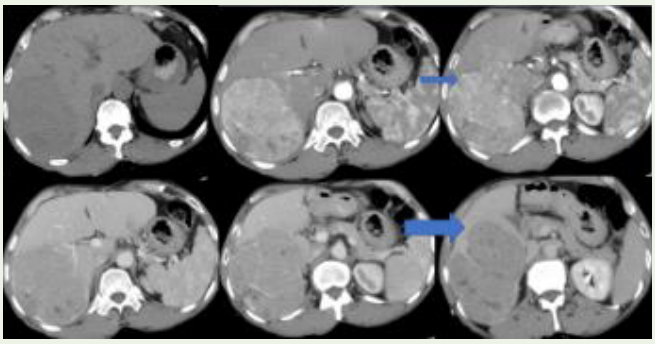

Figure 3: 63M, Intense homogenous arterial phase enhancement; Wash out in PV with corona enhancement in late arterial phase; Thin smooth capsular enhancement in equilibrium phase in well-differentiated carcinoma.

focus in dysplastic nodule giving rise to 'nodule within nodule' pattern. These changes occur in early phase HCC which subsequently progress to high grade HCC. When a nodule is dysplastic the normal arterial flow is reduced, and venous flow is maintained. With development of HCC there is arterialisation of blood supply and sinusoidal capillarization develops. There are new unpaired arteries which are not accompanied by bile ducts. Gradually the number of unpaired arteries increase which is proportionately increase with differentiation of HCC, particularly size less than 3 cms.

Typical CT features are not always observed in all HCC. In their study Lee et al observed that 56.4% of cases showed typical enhancement. It is also observed that 62.6% of moderately differentiated, 35.4% of well-differentiated, 52.3% of poorly differentiated HCC show classical pattern [14]. Well differentiated tumors receive portal blood flow whereas moderately differentiated tumors, poorly differentiated tumors, as well as tumor larger than 3cms are supplied by arterial blood [15].

Significance of capsular enhancement

Formation of fibrous capsule, which is a smooth, uniform and enhancing rim surrounding most of the nodules is a prominent feature of HCC (Figure 4). Presence of capsule indicates progressive HCC, not degenerative or regenerative nodules [16]. It is absent in early HCC and develop as a barrier for spread of tumor cells. Gradually it disappears due to tumor cell invasion. Hence its presence indicates tumor progression [17]. Since the significance of this capsular enhancement is not well-high-lighted in literature. We have analysed the capsular pattern in 5 cases of histopathologically proven Hepatocellular carcinoma (3 well differentiated, 2 moderately differentiated tumor) and discussed its importance in its evaluation. Capsular enhancement is seen 4 of 5 cases.

Differential diagnosis

Pseudo-capsule: Capsule is to be differentiated from pseudo-capsule which is peri-tumoral fibrosis and sinusoidal dilatation. This pseudo-capsule is thinner and show less enhancement. The distinction between capsule and pseudocapsule can only made in pathology. In at risk patients the capsular appearance has high predictive value of HCC regardless whether the rim enhancement represent capsule or pseudocapsule. 90% of HCC more than 5 cms in Asian population and 40% of non- Asians show capsule [18]. Presence of capsule or pseudocapsule differentiate HCC from dysplastic/regenerative

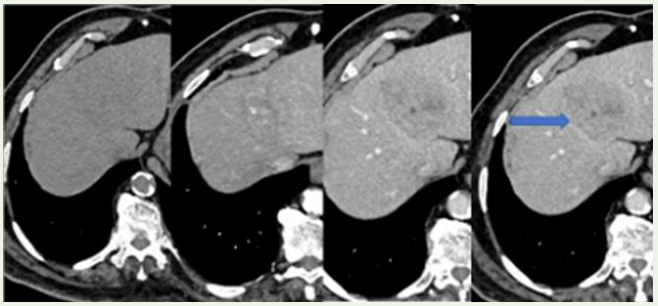

Figure 4: 60M, Delayed image showing capsular enhancement in moderately differentiated carcinoma.

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nodules. Fibrous capsule in HCC indicates favourable prognosis as it is associated with more effective trans-arterial chemo embolization and lower recurrence after resection or ablation due to barrier effect of tumor dissemination [17,19].

Corona enhancement: Capsular enhancement has also to be differentiated from corona enhancement which is due to transient rim enhancement of hypervascular HCC in arterial phase (Figure 5). This is due to vascular drainage of HCC. As the tumor cells proliferate rapidly the intra nodular and peri-nodular venous blood drains into surrounding sinusoid. Fibrous capsule that acts as a barrier gets interrupted and intra-tumoral blood drain into surrounding parenchyma via portal venules of the capsule. Hence, corona enhancement is seen in late arterial or portal phase when most of tumor show reduction of enhancement, not seen in equilibrium phase when the fibrous capsule enhances. It of variable in thickness and may be circumferential or eccentric or non-symmetric. This sign if present indicates HCC. This area corresponds to drainage pathway of tumor cells. Hence, this is the site of tumor recurrence or intrahepatic metastasis or daughter nodule [20].

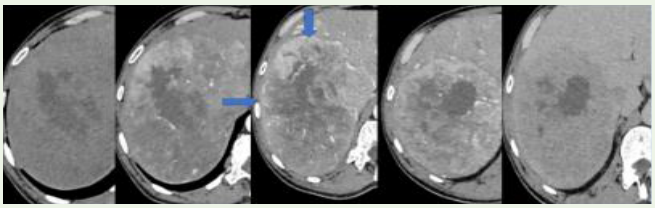

Figure 5: 45M, Eccentric partial corona-enhancement in delayed arterial phase and no capsular enhancement equilibrium phase in well-differentiated carcinoma.

Conclusions

Capsular enhancement is an interesting imaging finding, that can be observed in a significant number of HCC. Its true significance is not well-described in literature. Its clinical implication and the need to differentiate from pseudo-capsule are high-lighted in this review.

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