Nodule in Liver: Investigations, Differential Diagnosis and Follow-up

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Conventional ultrasonogram of the abdomen being noninvasive, inexpensive and ubiquitously available is the first imaging modality that raises suspicion of HCC in a patient with chronic liver disease with or without cirrhosis. The lesions in liver particularly nodule are being recognized with increased frequency with the wide spread use of ultrasonogram as the initial investigation and computerized tomography and magnetic resonance imaging subsequently. Any nodule in a cirrhotic liver should be considered as hepatocellular carcinoma until otherwise proved. This approach certainly is helpful in diagnosing HCC at its earliest possible stage to offer meaningful curative measures be it transplant, resection or ablative therapy. After a nodule is detected on ultrasonogram the next imaging modality can be a contrast enhanced study (dynamic CT scan or an MRI) to see if are present or not. Two vital clues for diagnosis of HCC by contrast enhanced imaging are presence of arterial hypervascularity and washout which are considered as “classical imaging features”. This sequence of events of arterial uptake followed by washout is highly specific for diagnosis of HCC by imaging. If the features are typical showing classical imaging features (i.e hypervascular in the arterial phase with washout in portal venous or delayed phase) the lesion should be treated as HCC *biopsy is not necessary*. Nodular lesions showing an atypical imaging pattern, such as iso- or hypovascular in the arterial phase or arterial hypervascularity alone without portal venous washout, should undergo further examinations with another contrast enhanced imaging. Biopsy is advisable for those lesions which do not show classical features on the imaging. (J CLIN EXP HEPATOL 2014;4:S57–S62)

The diagnosis of HCC is predominantly by imaging modality. Conventional ultrasonogram of the abdomen being noninvasive, inexpensive and ubiquitously available is the first imaging modality that raises suspicion of HCC in a patient with chronic liver disease with or without cirrhosis. This could happen either on surveillance or de novo. At times, particularly in young patients with vertically transmitted HBV infection in Asia pacific and African continents it is not uncommon to come across advanced HCC at the time first presentation. The lesions in liver particularly nodule are being recognized with increased frequency with the wide spread use of ultrasonogram as the initial investigation and computerized tomography and magnetic resonance imaging subsequently. The most important question to be answered

is to determine the nature of the nodule i.e. regenerating nodule, HCC, intrahepatic cholangiocarcinoma, metastatic lesion(s) or rarely an infective process. Any nodule in a cirrhotic liver should be considered as hepatocellular carcinoma until otherwise proved. This approach certainly is helpful in diagnosing HCC at its earliest possible stage to offer meaningful curative measures be it transplant, resection or ablative therapy. In this article we intend to answer two issues of practical importance. They are:

- If a nodule is detected on ultrasound how should it be investigated?
- If the nodule is negative for HCC how should it be followed

These recommendations will apply only to patients with liver cirrhosis of any etiology and those with chronic HBV

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Abbreviations: AASLD: American Association for Study of Liver Diseases; AFP: alphafetoprotein; ALT: alanine aminotransferase; APASL: Asia-Pacific Association for Study of Liver; AST: aspartate aminotransferase; CEA: carcino-embryonic antigen; CEUS: contrast enhanced ultrasound; CT: computerized tomography; DIA: digital image analysis; DW MRI: diffusion weighted magnetic resonance imaging; FDG: fludeoxyglucose; FISH: fluorescent in situ hybridization; FNA: fine needle aspiration; FNH: focal nodular hyperplasia; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; LDH: lactate dehydrogenase; MDCT: multidetector computerized tomography; MRI: magnetic resonance imaging; PEI: percutaneous ethanol injection; PET: positron emission tomography; PUO: pyrexia of unknown origin; RFA: radio frequency ablation; US: ultrasound

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infection without Definite cirrhosis. These guidelines may not necessarily apply to the general population.

IF A NODULE IS DETECTED ON ULTRASOUND HOW SHOULD IT BE INVESTIGATED?

After detecting a nodule in the liver in a cirrhotic patient the nodule requires to be characterized with multidetector computerized tomography, magnetic resonance imaging, contrast enhanced ultrasound or functional imaging of HCC by hepatocyte specific MRI, DW MRI, and Positron emission tomography (PET). Each technique has advantages and disadvantages. The choice of imaging modality depends upon many factors like number of nodules, presence or absence of cirrhosis, availability, expertise in interpretation and cost.

It is possible to diagnose HCC by noninvasive or semi invasive imaging modalities if typical imaging features are present¹⁻³ without a need for a biopsy. Firm diagnosis of HCC by imaging is important because it is noninvasive and hence easily acceptable to the patient. The probability of needle track tumor track seeding following a biopsy of HCC though small cannot be ignored. The reported incidence of needle tract tumor seeding after a biopsy is overall 2.7% or 0.9% per year.⁴ A retrospective review of 3636 image guided percutaneous core biopsies performed at a single center has revealed 0.5% of risk of significant hemorrhage related complications.⁵ The imaging modality further indicates delineation of extent of lesion, vascular infiltration, and effect on surrounding structures. This information is particularly useful in deciding the type of treatment like local ablative therapy (radiofrequency ablation RFA, PEI or Microwave ablation) resection or liver or liver transplant. The imaging modality selected should be widely available with reasonable expertise. For multiphasic computerized tomography for HCC the timing of scans is very vital and it has been recommended that imaging should be performed in specialized centre.⁶

After a nodule is detected on ultrasonogram the next imaging modality can be a contrast enhanced study (dynamic CT scan or an MRI) to see if “classical imaging features” are present or not.

CLASSICAL IMAGING FEATURES

Two vital clues for diagnosis of HCC by contrast enhanced imaging are presence of **arterial hypervascularity** and **washout** which are considered highly specific. HCC receives its vascular supply predominantly via hepatic artery. The arterial blood in the liver is diluted by portal venous blood which is devoid of contrast. HCC lesion being predominantly supplied by hepatic artery is not affected by this dilution. In contrast enhanced imaging arterial hypervascularity is defined as increased enhancement of the

lesion in the hepatic arterial phase relative to the background liver. Demonstration of this phenomenon requires a precontrast and a dynamic post contrast imaging of the liver. In the venous phase, the lesion of HCC enhances less than the rest of the liver. The next phase is “washout phase”. HCC lacks portal blood supply and the arterial blood flowing in the lesion does not contain the contrast any more while the rest of liver is opacified due to contrast containing portal blood. The classical imaging characteristics of this phenomenon are hypo attenuation on CT and hypo intense on MRI. The tracer kinetic modeling of a lesion with high proportion of intravascular space explains the dynamics of washout phase.⁷ The next phase is delayed phase where the presence of “washout” persists. At times the washout phenomenon can be seen only the delayed phase. In fact for demonstration of washout the delayed phase has been shown to be superior in the portal venous phase both for CT and MRI. The sequence of the events is fast and it is estimated that this occurs at 2–3 min following injection of intravenous contrast agent.^{8,9} This sequence of events of arterial uptake followed by washout is highly specific for diagnosis of HCC by imaging.¹⁰⁻¹² A four phase study (precontrast, or unenhanced, arterial, portal venous and delayed phase) as its sometimes called is required to properly ascertain the existence of HCC by imaging. These features are so specific that the dynamic sequence is referred to as “classical imaging features”.¹³ It is recommended that strict application of diagnostic criteria regarding hypervascularity and washout is essential. The presence of hypervascularity alone is not sufficient and washout is also essential. This also helps in differentiating intrahepatic cholangiocarcinoma which shows delayed enhancement.¹⁴ Both AASLD guidelines and APASL guidelines are in complete agreement on the definition of imaging features of “classical imaging features”.¹⁵ It is essential to note that the application “classical imaging features” by dynamic imaging criteria should be applied only to patients with cirrhosis of any etiology. With respect hepatitis B related HCC the patients can be in chronic hepatitis phase without any fully developed cirrhosis or even a regressed cirrhotic state.¹⁶ Since imaging plays a vital and decisive role in the diagnosis of HCC it is crucial that imaging be properly done adhering to strict protocols namely type of equipment, the amount of contrast used method of administering, timing of studies and thickness of slices to be obtained.

Does size of the lesion seen in the initial ultrasound examination matter?

There is difference of opinion about this aspect.

Nodules Less Than 1 cm

Majority of nodules less than 1 cm arterially enhancing are quite common in cirrhosis and majority of them are benign. However some of these have the potential to

become malignant over course of time. Although CT and MRI have as sensitivity of 60–94% and 58.5–93% sensitivity respectively, for nodules larger than 1 cm their sensitivities are reduced to 33–45% and 33–67% respectively for nodules less than 1 cm. One way to resolve this issue is to follow by ultrasonogram till they grow beyond 1 cm or diminish or vanish or remain static. Diagnosing such small nodules in cirrhosis is quite difficult and challenging. Biopsy of these small nodule is fraught with problems like difficulty in obtaining adequate tissue, sampling errors, interpretational errors. A dysplastic nodule is difficult to be differentiated from fully evolved HCC¹⁷ and a negative biopsy does not rule out malignancy

For nodules less than 1 cm found on ultrasound examination AASLD guidelines (2010) recommend 3–6 monthly follow-up with ultrasound (level III) for a period of at least 2 yrs.

Nodules More Than 1 cm

Validation information is available for lesions more than 1 cm. MR imaging has been shown to have a specificity of 96.6% and positive predictive value of 97.4%.¹⁸

For lesions above 1 cm detected on ultrasound screening of cirrhotic liver AASLD 2010 guidelines recommend either Multidetector CT scan or dynamic MRI as the subsequent imaging modalities. If the appearances are typical of “classical imaging features” on either CT scan or MRI no further investigation is required and the diagnosis of HCC is confirmed. If the findings are not classical (and do not suggest hemangioma) then either a second imaging modality can be done or a biopsy can be performed (level II).

In contrast, APASL¹⁹ (2010 ref) recommendations are “regardless of size” and contrast enhanced ultrasound (CEUS) finds a place in the recommendation.

Dynamic CT or dynamic MRI is recommended as a first-line diagnostic tool for HCC when a screening test result is abnormal. Hallmark of HCC during CT scan or MRI is the presence of arterial enhancement, followed by washout of the tumor in the portal venous and/or delayed phases.

Typical HCC can be diagnosed by imaging regardless of the size if a typical vascular pattern, i.e., arterial enhancement with portal venous washout, is obtained on dynamic CT, dynamic MRI, or CEUS.

IF THE NODULE IS NEGATIVE FOR HEPATOCELLULAR CARCINOMA HOW SHOULD IT BE FOLLOWED DEPENDING ON SIZE AND NATURE?

The major difference in AASLD and APASL guidelines is approach to lesions that do not demonstrate classical imaging features.

It appears that the reasons for atypical features are 1. Size of the lesion and 2. The nature of the lesion i.e. differentiation, although these two are interdependent.

Classical features may be absent in larger lesions also. Yu et al demonstrated that in patients with HBV induced HCC, lesions with spherical contour greater than 2 cm were found to have high malignant potential and lacked arterial hypervascularity.²⁰ The explanation for this feature may be presence of central necrosis or lesion heterogeneity (nodule-in-nodule appearance). The “early” HCCs have been shown to have fewer portal tracts and fewer arterioles.²¹ 41–62% of lesions smaller than 2 cm showed either absence of arterial hypervascularity, venous washout or both.^{22,23} Majority of cirrhotic nodules smaller than 1 cm are benign.¹⁶ Whether this applies to the situation with HBV related HCC is questionable. Hypervascular lesions smaller than 1 cm in mild cirrhosis related to HBV has HCC²⁴ reemphasizing the importance of hypervascularity even in smaller lesions. Smaller lesions are well differentiated and 87% of well differentiated lesions showed either absence of arterial hypervascularity, venous washout or both.^{22,23}

ATYPICAL IMAGING FEATURES (NODULE NOT SHOWING CLASSICAL FEATURES ON INITIAL IMAGING)

APASL guidelines differ from AASLD guidelines regarding those lesions showing atypical imaging (lesions showing hypervascularity but no washout). Two other imaging modalities are suggested with a principle that malignant lesions can be reliably differentiated from on timorous liver based on the fact malignant lesion does not contain Kupffer cells. Kupffer cell density is considered as a surrogate marker for benignity. One is contrast enhanced ultrasonogram using perfluorobutane microbubbles (sonozoid, GE Healthcare) mainly available in Japan. The other is MR contrast agent super paramagnetic iron oxide (SPIO) namely ferucarbotran (Resovist, Bayer) and ferumoxide (Feridex, AMAG Pharmaceuticals).¹⁹ Nodular lesions showing an atypical imaging pattern, such as iso- or hypovascular in the arterial phase or arterial hypervascularity alone without portal venous washout, should undergo further examinations. Contrast-enhanced US (CEUS) is as sensitive as dynamic CT or dynamic MRI in the diagnosis of HCC.¹⁹

AASLD (2011) on the other hand recommends other contrast study (if initial was MDCT, to apply contrast enhanced MRI and vice versa) for those lacking hypervascularity AND washout in venous or delayed phase in the initial study. Biopsy is recommended once a contrast study does not show classical features either on initial examination or subsequent examination.¹⁶ Contrast enhanced US is not favored in the AASLD guidelines because it may be associated with false positive HCC diagnosis in

patients with cholangiocarcinoma and has been dropped from diagnostic techniques.¹⁶

CLINICAL DIFFERENTIAL DIAGNOSIS OF NODULE IN THE LIVER CIRRHOSIS

The importance of an accurate history and physical examination in diagnosis and treatment for solid liver mass that too occurring in cirrhotic individual cannot be overemphasized. Use of oral contraceptives or anabolic steroids can be related to hepatic adenoma. Primary sclerosing cholangitis, Caroli's disease and choledochal cysts are known to be associated with cholangiocarcinoma. A previous neoplasm or chemotherapy increases the suspicion of metastatic disease. Physical examination should look for liver tenderness, lymphadenopathy, hepatomegaly, splenomegaly, ascites, other stigmata of chronic liver disease, or general deterioration signs (fever, weight loss). High alkaline phosphatases, high lactate dehydrogenase (LDH), low albumin, high prothrombin time, and iron overload are non specific but may suggest underlying cirrhosis or an infiltrative process. A liver mass in a cirrhotic liver should be viewed as an HCC until proven otherwise.

Malignant lesions	Benign lesions
Hepatocellular carcinoma	Hemangioma
Dysplastic nodule	Hepatic adenoma
Cholangiocarcinoma	Focal fatty infiltration of the liver
Liver metastases	Hepatic cyst
Lymphoma (rare)	Focal Nodular Hyperplasia (FNH)
	Amoebic liver abscess
	Pyogenic liver Abscess
	Fungal Hepatic Abscesses
	Hydatid Cyst

MALIGNANT LESIONS

Hepatocellular Carcinoma

HCC is a common tumor in a cirrhotic individual occurring with an annual incidence of 1–6%.²⁵ The common risk factors are cirrhosis, alcohol, HBV, HCV, metabolic liver diseases and hormonal treatments.²⁶ Majority of HCC arise in cirrhotic liver although recently there is increased awareness of HCC occurring without cirrhosis in non alcoholic fatty liver disease.²⁷ New onset abdominal pain, rapidly enlarging liver, PUO, weight loss and rarely hemoperitoneum in a cirrhotic should arouse suspicion of HCC. Common laboratory results that are associated with development of HCC in a cirrhotic are sudden increase in alkaline phosphatase, increased AST/ALT and erythrocytosis. Occasionally one may across para-neoplastic manifestations in the form of hypoglycemia, hypercalcemia, hypercholesterolemia and persistent leukocytosis.

Dysplastic Nodule

One of the most difficult diagnostic dilemmas one comes across when one faces a small nodule in a cirrhotic is dysplastic nodule. Dysplastic nodules can be of low or high grade dysplasia. A regenerative nodule can. Progress to well differentiated or even poorly differentiated HCC through stages of low grade dysplasia, and then high grade.²⁸ On MRI imaging the dysplastic nodules are usually iso- or hypo- intense lesions where as HCC is hyper intense. Histology is required in some cases although there are limitations like failure to obtain tissue, sampling problems etc. If HCC cannot be confirmed on biopsy, a wait and close follow-up with repeat imaging is all what is possible.

Cholangiocarcinoma

The risks for development of cholangiocarcinoma are cirrhosis, primary sclerosing cholangitis (PSC, 10%), bile duct adenoma, choledochal cysts, Caroli's disease and liver fluke. The most frequent clinical presentation is rapidly increasing bilirubin associated to weight loss. Peripheral or intrahepatic cholangiocarcinoma which constitute 15% of all cholangiocarcinoma closely resemble HCC without cirrhosis.

Tumor markers CEA, CA 19-9 or AFP may be elevated. The combination of Ca 19-9 + CEA markers gave an accuracy of 86% in diagnosis of cholangiocarcinoma.²⁹ Digital image analysis (DIA) and fluorescent in situ hybridization (FISH) are more sensitive than routine standard brush cytology in the diagnosis of cholangiocarcinoma.

Liver Metastasis

The most common site of metastasis from the gastrointestinal tract, pancreas, breast, and lung is the liver. Liver metastasis is a rare finding in cirrhosis. Bilobar involvement is frequent and only 20% of liver metastases present as solitary lesions. During the early vascular phase of dynamic CT, metastasis appears with increased enhancement. The sensitivity of CT (85%) can be augmented by CT arterial portography. PET CT with FDG is most useful imaging modality with accumulation in cells with hyper metabolism. The sensitivity and specificity of staging for Colon, lung, and breast malignancies with PET CT is 92–100% and 85–100% respectively.³⁰ CT Porto angiography is one of the most sensitive imaging for metastasis but it is an examination that is performed in high selected cases, in few institutions and not for all types of liver lesions. Guided FNA will help identifying the primary lesion.

BENIGN “NODULE” LESIONS IN CIRRHOSIS

Focal Fatty Infiltration of the Liver

With increasing obesity, diabetes and metabolic syndrome world wide it is not uncommon to find focal accumulation and sparing of fat in the liver that mimics a nodule in 10%

of patients with fatty liver. Fat accumulates focally or shows focal sparing. This feature occurs usually in the anteromedial segment of the left lobe. On US, fat is hyper-echoic. On CT, it has low attenuation. Displacement of intrahepatic vessels is not a feature of focal fatty sparing.

Hemangioma

Hemangioma is found in 20% of the general population, more commonly in women. The majority are asymptomatic. Symptoms are rare and may include abdominal pain, early satiety, anorexia, nausea in Giant hemangioma (more than 4 cm). Contrast enhanced CT or MRI are the best modalities for the diagnosis.

Hepatic Adenoma

Adenoma occurs in women with oral contraception use more than 5 years or in diabetic patients. The lesion is hypo- to hyper-echoic on US and hypo- to hyper-dense on CT. MRI is not specific. The lesions are often smaller than 8 cm but may be larger than 15 cm. Five percent of hepatic adenomas transform to HCC. Beta-catenin immunostaining may be useful for diagnosis.

SUMMARY

If a Nodule is Detected on Ultrasound How Should it be Investigated?

- 1 Four phase (sometimes called triphasic) contrast enhanced computerized tomography or dynamic MRI to be done in centers equipped with appropriate equipment and expertise
- 2 If the features are typical showing classical imaging features (i.e. hypervascular) in the arterial phase with washout in portal venous or delayed phase the lesion should be treated as HCC *biopsy is not necessary*

If the Nodule is Negative for Hepatocellular Carcinoma How Should it be Followed Depending on Size and Nature ?

Nodular lesions showing an atypical imaging pattern, such as iso- or hypovascular in the arterial phase or arterial hypervascularity alone without portal venous washout, should undergo further examinations with another contrast enhanced imaging. Biopsy is advisable for those lesions which do not show classical features on the imaging.

CONFLICTS OF INTEREST

The author has none to declare.

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