Benign versus malignant nodules in the cirrhotic liver

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Learning objectives

-to improve knowledge regarding the imagistic features of cirrhosis-associated hepatocellular nodules.

-to be able to distinguish between regenerative nodules, dysplastic nodules and hepatocellular carcinoma.

-to illustrate pearls and pitfalls regarding the enhancement pattern of benign and malignant lesions in the cirrhotic liver.
Background

Cirrhosis is the common end-point of chronic liver disease and is characterized by diffuse fibrosis, nodular regeneration, distortion of hepatic architecture and perfusion abnormalities. A cirrhotic liver may display a wide range of lesions and their characterization may be difficult. It is radiologist’s responsibility to be able to recognize such lesions and to early detect small hepatocarcinoma (HCC).

The differentiation between benign and malignant cirrhosis-associated nodules is primarily based on vascularity pattern. Benign nodules have portal venous blood supply while malignant nodules have arterial blood supply. However, the diagnosis of cirrhotic-associated nodules based on dynamic imaging techniques is sometimes challenging because these nodules show a continuum of vascular pattern alterations. The main goal of screening in cirrhotic patients is early detection of HCC. Early HCC means a lesion that is less than 2 cm diameter, with a 5-year survival rate of 89% [1].

The most common lesions seen in the cirrhotic liver are:

**Regenerative nodules**

Regenerative nodules are the most common nodules found in the cirrhotic liver. They are the result of hepatic necrosis and altered circulation and appear as round, well-defined nodules delimited by bridging fibrosis. These nodules have normal hepatocellular function and portal vascularization. Most of them are less than 2 cm in diameter; regenerative nodules of more than 2 cm diameter have been seen in patients with Budd Chiari syndrome.

**Dysplastic nodules**

Dysplastic nodules are regenerative nodules but with atypical cells; they do not show clearly signs of malignancy. Histologically, low-grade dysplastic nodules have progressive architectural distortion, minimal cytologic atypia and a variable number of unpaired arterioles [1]. Low-grade dysplastic nodules have low malignant potential. High-grade dysplastic nodules have more advanced cytologic atypia and an important number of unpaired arterioles; these nodules are thought to progress to hepatocellular carcinoma more frequently than low grade dysplastic nodules. Histologically, a high-grade dysplastic nodule is very similar to a well-differentiated hepatocellular carcinoma. Dysplastic nodules show a loss of portal vascularization.

**Hepatocellular carcinoma**
Hepatocellular carcinoma is a malignant neoplasm that contain dedifferentiated hepatocytes. Histologically, hepatocellular carcinoma is characterized by advanced parenchymal alterations, cytologic atypia, necrosis and an increased number of unpaired arterioles. It has the potential to invade blood vessels and to metastasize.

**Hepatic perfusion disorders**

There are many causes for hepatic perfusion disorders in the cirrhotic liver such as: arteriportal shunts, steal phenomen, portal vein occlusion or vascular variations. Liver cirrhosis and HCC are the most common causes for hepatic perfusion disorders. [2]
Findings and procedure details

This review illustrates the CT and IRM aspect of regenerative nodules, dysplastic nodules and hepatocarcinoma in the cirrhotic liver along with the differential diagnosis of such lesions.

Procedures

For the evaluation of the benign or malignant nodules on the cirrhotic liver, we used multislice CT and IRM examination.

Multislice CT examination included pre-contrast and contrast CT with three phases: arterial, portal and delayed phase to detect hypervascular nodules and to evaluate the wash-out curve. 100 ml of non-ionic contrast material was injected into an antecubital vein with a flow of 3 ml/sec. The CT-timing was as follows: 25-35 sec for the arterial phase, 60-70 sec for the portal phase and 180 sec for the delayed phase.

MR imaging was performed with a 1,5 T imager and consisted of pre-contrast and post-contrast enhanced T1 and T2-weighted images acquired in the axial and coronal plane using FSE/TSE pulse sequences. For contrast imaging, 0,1 mmol/kg of body weight dose of Gd-BOPTA (MultiHance) (0,2 ml/kg of body weight) was administered into the arm at 2ml/sec using a power injector followed by 20 ml flush of normal saline. The scan delays for dynamic imaging were 30, 60, 180 sec after contrast administration. DWI images were acquired with an axial echo-planar diffusion weighted sequence (TE 80, TR 3800) using a respiratory triggered technique with values of b of 50, 400, 800 sec/mm².

Image findings

Regenerative nodules (Fig. 1, Table 1)

Regenerative nodules may or may not be seen on CT or RM imaging. At non-contrast CT imaging, regenerative nodules are rarely visible; siderotic nodules may appear hyperdense to liver parenchyma due to iron content. At contrast CT imaging, regenerative nodules do not show arterial enhancement; on portal and delayed phases, they enhance as the normal liver parenchyma.

At pre-contrast RM imaging, regenerative nodules appear with variable signal intensity on T1-weighted images and iso- or hypointense T2-weighted images. If the regenerative
nodules contain important amounts of fat, copper or proteins, they will appear hyperintense T1. A steatotic regenerative nodule appears with high signal on in-phase gradient images and shows a loss of signal on out-of-phase gradient images. A siderotic nodule will appear hypointense on T1 and T2-weighted images. Although a T1 hyperintense nodule usually suggests a benign nodule, it has been reported that HCC lesions may also demonstrate hyper-T1 intensity [3]. At contrast RM images, regenerative nodules enhance a little less or as much as liver parenchyma because they have portal vascularization. After administration of hepatobiliary-specific or SPIO contrast material, on delayed-T1 images, regenerative nodules have the same enhancement pattern as the surrounding liver parenchyma.

**Dysplastic nodules (Fig. 2, Table 2)**

At unenhanced CT imaging, dysplastic nodules usually appear hypoattenuating, even though they may also appear iso- or hyperattenuating to the liver parenchyma. At contrast-enhanced CT imaging, dysplastic nodules may show early arterial uptake but **they do not show wash-out** on portal or delayed phases.

At unenhanced RM imaging, dysplastic nodules have variable appearances. On T1-weighted images, both low- and high-grade dysplastic nodules may display a low, intermediate or high signal. On T2-weighted images, low-grade dysplastic nodules usually have a low signal, while high grade dysplastic nodules have a more intense signal.

At contrast-enhanced RM imaging, low-grade dysplastic nodules closely resemble to regenerative nodules, while high grade dysplastic nodules resemble to well-differentiated hepatocellular carcinoma.

**Hepatocellular carcinoma (Table 3, Fig. 3, Fig. 4, Fig. 5, Fig. 7, Fig. 8, Fig. 12, Fig. 14)**

80-90% of HCCs are hypervascular and show a typical enhancement pattern on contrast imaging. According to AASLD (American Association for the Study of Liver Diseases) guidelines for non-invasive diagnostic criteria of HCC, the hepatocarcinoma radiological hallmark is contrast uptake in the arterial phase and wash-out in the portal/delayed phase [4]. This enhancement pattern is explained by the fact HCC is supplied by the hepatic artery rather than the portal vein. Thus, at enhanced-CT imaging, hepatocellular carcinoma should show an intense arterial uptake and then a rapidly wash-out. Other features of HCC is late capsule enhancement and portal vein invasion.

However, we must note that there is a variation in enhancement in small versus large HCC: small HCC has an homogenous enhancement, while large HCC (> 5 cm), has a more heterogenous enhancement (mosaic pattern).
MRI has a better sensitivity and specificity than CT in detecting HCC, especially if the tumor is less than 2 cm in diameter [5]. At unenhanced RM imaging, hepatocellular carcinoma may show an iso- or high signal on T1-weighted images. High signal on T1-weighted images may be explained by intratumoral fat or protein or by low intensity of the surrounding liver parenchyma. On T2-weighted images HCC is hyperintense. After gadolinium administration, HCC show arterial enhancement and rapidly wash-out on portal phase. After hepatobiliary contrast agents administration, HCC does not enhance as the normal liver parenchyma does. On hepatobiliary-phase, HCC appear as a hypointense lesion as it is composed of altered hepatocytes. On DWI, HCC is hyperintense in comparison with the surrounding liver parenchyma, while dysplastic nodules are hypo- or isointense.

**Atypical HCC (Fig. 6)**

There have been described hypovascular and isovascular HCC, which are more difficult to detect because there is minimal or no enhancement on arterial phase. In these cases, attention should be paid on wash-out seen on portal and/or delayed phases.

Differential diagnosis

**Hepatic perfusion disorders (Fig. 9)**

At non-contrast CT examination, the hepatic perfusion disorders (HPD) appear as a wedged-shaped, low attenuation areas. On contrast CT images, they are hyperattenuated on arterial phase and isoattenuated on portal phases. Plain MR scan shows an area of iso-intensity on T1 and T2-weighted images. Contrast IRM examination has similar characteristics as contrast CT scan.

Hepatic perfusion disorders may appear as enhancing nodules on arterial phase and may be mistaken for HCC in cirrhotic patients. Attention should be paid on wash-out seen on portal or delayed phases and to lack of hyperintensity on T2 weighted images. SPIO-contrast IRM examination may also help differentiate hepatic perfusion disorder from HCC: no loss of signal in HPD.

**Cholangiocarcinoma (Fig. 10, Fig. 11)**

Cholangiocarcinoma is a malignant tumor derived from cholangiocytes of the biliary tree. Cholangiocarcinoma is the second most common primary malignancy after hepatocellular carcinoma in the cirrhotic patients [6]. At non-contrast CT, cholangiocarcinoma appears as a low attenuation lesion; at contrast imaging,
cholangiocarcinoma shows a peripheral rim-like enhancement during arterial phase and a centripetal progressive enhancement during portal and delayed phases. Thus, a progressive contrast uptake with no wash-out should indicate a cholangiocarcinoma rather than a hepatocellular carcinoma.

**Focal confluent fibrosis (Fig. 13)**

Confluent fibrosis is related to the natural process of cirrhosis and a common finding in alcohol-related cirrhosis [7]. Focal confluent fibrosis is associated with capsular retraction and appears as a wedge-shaped area of iso- or hypoattenuation on non contrast CT. After contrast administration, the fibrosis will show progressive enhancement. At RM imaging, it is hypointense on T1 and moderate hyperintense on T2-weighted images.
Fig. 1: CECT examination shows liver cirrhosis with heterogenous parenchyma. A relatively well-defined, 15 mm hepatic nodule is seen in segment VII, with no enhancement on contrast imaging, consistent with regenerative nodule (A, B). Focal confluent fibrosis (orange arrows, A, B). Another hepatic nodule measuring 28/25 mm, is seen in segment III, with arterial uptake (C) and wash-out in portal phase (D), consistent with hepatocellular carcinoma. Marked ascites (green star, F), splenomegaly, splenic infarcts (yellow arrows, F) and collateral pathway circulation (E).

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Regenerative nodules: CT and IRM features

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<th>MRI</th>
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<td>-non-contrast: iso/hypo/hyperintense T1; iso/hypointense T2</td>
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<tr>
<td>-contrast: no arterial uptake, no ‘wash-out’</td>
<td>-T1+C (Gd): no enhancement</td>
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**Table 1:** Regenerative nodules: CT and MRI features

Fig. 2: Dysplastic nodule in a cirrhotic patient. IRM examination shows a 15 mm, T1 and T2- isointense hepatic nodule in segment II (A, B). Axial contrast-enhanced MR image obtained in the hepatic arterial phase shows peripheral rim enhancement of the nodule (C). Axial contrast-enhanced RM obtained in the equilibrium phase shows no wash-out (D). DWI demonstrates no diffusion restriction in segment II; however, there is a spot of restricted diffusion in segment IVB, with no correspondent on T1-weighted images (E). Perihepatic ascites (B, yellow star). Collateral pathways (D, orange arrows).

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<td>-non-contrast: iso/hypo/hyperintense T1; iso/hypointense T2</td>
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<td>-contrast: arterial uptake, no ‘wash-out’</td>
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<td>-T1+C (Gd): arterial uptake, no ‘wash-out’</td>
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**Table 2:** Dysplastic nodules: CT and MRI features

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Fig. 3: IRM examination in a cirrhotic patient shows an ill-defined nodular lesion, measuring 35/30 mm, located in segment VIII, with low signal intensity in T1-weighted images (A) and high signal intensity in T2-weighted images (B). The lesion demonstrates moderate arterial enhancement (C) and wash-out on delayed phase (D). Intratumoral high signal on DWI sequence (E). Tumour thrombus in the right portal vein (yellow arrow, F). Note the presence of another lesion located in the pancreatic tail, T1-hypointense, T2-hyperintense, with moderate enhancement and restricted diffusion (orange arrow, F). Histology: moderately differentiated HCC and pancreatic ductal adenocarcinoma.

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### Hepatocellular carcinoma: CT and MRI features

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<td>-non-contrast: iso/hyperintense T1, hyperintense T2</td>
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<td>-contrast: arterial uptake, early ‘wash-out’</td>
<td>-T1 + C (Gd): arterial uptake, early ‘wash-out’</td>
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<td>-T2 + C (SPION): hypointense</td>
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<td>-DWI: hyperintense</td>
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**Table 3:** Hepatocellular carcinoma: CT and MRI features

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Fig. 4: HCC in a cirrhotic liver with portal hypertension and marked splenomegaly. NECT examination demonstrates a slightly hypodense liver nodule, with irregular border, located in the segment VI (A), with intense arterial uptake (B) and rapid wash-out on portal phase (C) D. Perihepatic ascites (blue star). E. Porta hepatis enlarged lymph nodes (yellow arrows). F. Splenomegaly (blue star).

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Fig. 5: IRM examination demonstrates a 17 mm hepatic nodule, located in segment V, which is hypointense on T1-weighted images (A). Axial contrast-enhanced RM examination shows intense uptake of the nodule in the hepatic arterial phase (B) and wash-out in the delayed phase (C), consistent with hepatocellular carcinoma. On DWI, the lesion shows restricted diffusion (D).

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Fig. 6: Hypovascular hepatocellular carcinoma. NECT and CECT examination shows an enlarged liver, splenomegaly (orange star, A), and discrete collateral pathway circulation. CECT shows a 30/35 mm isoattenuated hepatic nodule in segment VII (C), with hypoattenuation on portal (D) and delayed phase (E), consistent with hypovascular hepatocellular carcinoma. No arterial enhancement is seen. Porta hepatis enlarged lymph nodes (orange arrows, F). Histology: Well-differentiated hepatocellular carcinoma.

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**Fig. 7:** HCC in a patient with cirrhosis and portal hypertension. IRM examination demonstrates an ill-defined nodular lesion located in segment VIII. T1-weighted images show hypointensity of the lesion compared with the surrounding liver parenchyma (A, B). Arterial enhancement following gadolinium (C) and wash-out on delayed phase (D). There is diffusion restriction (E). Another hepatic nodule in segment V, with similar enhancement pattern (orange arrow, F). Splenomegaly (F) and porto-systemic collateral pathways (permeabilisation of umbilical vein- green arrow, F).

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Fig. 8: Multifocal HCC in a patient with alcoholic cirrhosis. NECT and CECT scan shows multiple liver nodules located in segments VI, VII and VIII, with low attenuation on non-contrast CT scan (A), heterogenous arterial enhancement (B) and wash-out on delayed phase (C). Splenomegaly and perisplenic and perigastric varices (D). Department of Radiology and Medical Imaging, 'Carol Davila' Central Military Emergency University Hospital, Bucharest, Romania.

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**Fig. 9:** Arterioporal shunts in a cirrhotic patient. Multiple focal hepatic lesions, randomly distributed, with the same attenuation with the liver parenchyma on non-enhanced CT examination (A). At contrast-enhanced CT images, these lesions are hypervascular on arterial phase (B, C) and become isodense on delayed phase (D).

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**Fig. 10:** Intrahepatic cholangiocarcinoma in a cirrhotic patient. Coronal contrast-enhanced CT image shows a cirrhotic liver with enlarged left lobe (orange star) and ascites (green arrowhead) (A). Axial contrast-enhanced CT images reveal a 11/6.5 cm ill-defined mass in segments VII and VIII, with capsular retraction and with discrete enhancement in the delayed phase (B, C, D). Invasion of right hepatic vein (E). Porta hepatis enlarged lymph nodes (F). Fig. 11: At IRM examination, the mass is T1-hypointense (G) and slightly T2-hyperintense to the liver parenchyma (H). At diffusion weighted sequence, there is restricted diffusion (I). Invasion of right biliary hepatic ducts and enlarged left hepatic ducts (J).

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**Fig. 11:** Intrahepatic cholangiocarcinoma in a cirrhotic patient. Coronal contrast-enhanced CT image shows a cirrhotic liver with enlarged left lobe (orange star) and ascites (green arrowhead) (A). Axial contrast-enhanced CT images reveal a 11/6.5 cm ill-defined mass in segments VII and VIII, with capsular retraction and with discrete enhancement in the delayed phase (B, C, D). At IRM examination, the mass is T1-hypointense (G) and slightly T2-hyperintense to the liver parenchyma (H). At diffusion weighted sequence, there is restricted diffusion (I). Invasion of right biliary hepatic ducts and enlarged left hepatic ducts (J).

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Fig. 12: Multifocal HCC with invasion of portal vein. NECT and CECT examination shows extensive HCC in a cirrhotic liver. Multiple heterogeneous hypoattenuated masses (A), located in both the right and left lobe of the liver, with early arterial uptake (B) and rapid wash-out (C). These lesions are heterogeneous with enhancing rim and areas of hypoattenuation consistent with necrosis. Invasion of the left portal vein (D).

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Fig. 13: Focal confluent fibrosis in a cirrhotic patient with ascites. Non-contrast CT demonstrates a slightly hypoattenuated nodule in segment VIII (A). After contrast administration, there is a minimal enhancement on delayed phase (D). Note that there is no arterial enhancement (B) and no wash-out (C, D). Ascites (yellow star, A).

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Fig. 14: Diagnostic algorithm for suspected HCC, according to AASLD (American Association for the Study of Liver Diseases). CT, computed tomography; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasound.
Conclusion

Cross-sectional CT and IRM imaging is a key step in evaluating hepatic nodules in the cirrhotic liver. Knowledge of the most common pitfalls helps to maintain high specificity and accuracy of diagnostic interpretations of hepatic nodules in the cirrhotic liver.
References


