A. Assessment of diffuse liver disease (including cirrhosis)

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Learning objectives

• To learn the imaging features of cirrhotic diffuse liver disease.
• To learn the imaging features of non-cirrhotic diffuse liver disease.
• To learn how imaging can help in the quantification and follow-up of diffuse liver disease.
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**Fig. 0:** Figure 2

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Main

DEFINITION

Hepatic cirrhosis is a chronic inflammatory liver disorder associated with irreversible fibrosis. Although fibrosis is considered the hallmark of cirrhosis, regeneration, necrosis and inflammation are important prognostic factors. Cirrhosis is also frequently associated with steatosis, iron overload and prominent vascular abnormalities (Figure 4).

The most relevant etiologic factors are alcohol, viruses, nonalcoholic steatohepatitis and hemochromatosis. Initial clinical symptoms are vague while advance disease is mainly associated to liver decompensation with ascites, digestive hemorrhage, jaundice and hepatic encephalopathy. Hepatocellular carcinoma (HCC) development rate is 8% at 5 years and 25% at 10 years.

Patients with chronic hepatitis and cirrhosis are initially biopsy to establish a definitive diagnosis and stage the liver status. MR imaging is used in most centers for diagnosing tumor development because of its ability to reliably depict HCC.

The currently available imaging tests (US, CT and conventional MR imaging) are neither sensitive nor specific for early parenchymal changes. Many signs of moderate and advanced cirrhosis can be detected as morphological changes. New functional MR imaging sequences can also depict fat and iron deposition, regenerative nodules, necroinflammatory infiltrate, fibrosis, varices, perfusion abnormalities and hepatocyte functionality (Figure 5).

Evaluating chronic hepatitis and cirrhosis with imaging modalities should be performed on early stages of the disease. To be clinically useful, any method used to evaluate chronic hepatitis and cirrhosis must accurately identify regeneration, inflammation, necrosis, fibrosis, fat, iron and also neoplasia. Fibrosis, necroinflammatory activity, fat and iron deposits are the most important parameter for antiviral treatment indication and follow-up.

MR TECHNIQUE

High resolution expiratory breath hold dual echo chemical shift spoiled GRE sequence is used for opposed-phase and in-phase T1W images. The dual echo sequence can evaluate fat, although the use of T2* correction performs better. This T2* calculation can be used to accurately measure iron with a multiecho GRE sequence.

Respiratory triggered STIR TSE images should be optimized so that the signal intensity of the liver is close to that of the subcutaneous fat and paraspinal muscles (TI of 150-160
msec at 1.5 Tesla and 180-190 at 3 Tesla magnets), which serve as an internal tissue of reference for the necro-inflammatory activity.

3D spoiled T1W GRE contrast-enhanced dynamic examinations with fat suppression are mainly used to exclude tumor development and grade esophageal varices. Controlling the bolus arrival interval, the late arterial, portal and equilibrium phases are acquired. MIP vascular map images reconstructed from the arterial and portal phases show the extent of collaterals vessels due to portal hypertension, as well as the arteries that perfuse abnormal regions and lesions.

In order to calculate pharmacokinetic model (PKM) parameters, the acquisition should have enough temporal resolution (less than 5 seconds each image set, during at least 5 minutes) with a dual input double compartment model and voxelwise statistical analysis is suggested. This PKM acquisition can be acquired with a low dose of contrast media (a fifth of the regular dose) and be also used to calculate the bolus arrival time to properly initiate the late arterial phase of the high resolution conventional dynamic sequence.

The 3D high resolution fat suppression T1W spoiled GRE images obtained 30 to 60 minutes after the administration of hepatobiliary contrast media (HBCM), although not routinely use in the MR evaluation of cirrhosis and HCC development, may give information on hepatocyte functionality.

The T2* GRE images obtained after SPIO liver enhancement, with and without concomitant gadolinium based contrast-enhanced dynamic images, can be used to rule out HCC in difficult cases and depict advance fibrosis. Both types of specific contrast media with intracellular phases may be used to differentiate perfusion abnormalities from tumor development.

Although large vessels can be observed with most MR images, the use of Steady State Fully Refocused transverse magnetization GRE images (such as Balanced, Fiesta or True-FISP) facilitates the observation of abnormal parenchyma vessels.

In order to standardize DW acquisitions and ADC calculations, a biexponential signal modeling and respiratory-triggered precontrast acquisitions with 5 b-values (0, 50, 200, 400 and 1,000 s/mm²) is suggested.

**IMAGING REGENERATION**

Chronic hepatitis does not modify the macroscopic architecture of the liver while advanced cirrhosis generates typical morphologic changes in the liver parenchyma and surface contour by changing the liver architecture due to regenerating nodules, necrosis and fibrous development.
Liver surface nodularity is usually fine and diffuse, being more prominent on the hypertrophied segments. Although the finding has been claimed as characteristic, minor bulging of the liver surface can be found in normal cases and, also, hepatic surface nodularity can be seen in patients with fulminant hepatic failure usually reflecting a combination of alternating foci of confluent regenerative nodules and necrosis.

Most specific, regeneration and necrosis leads to liver global or segmental volumetric changes associated with regional variations in the portal venous blood supply. Although any combination can be found, the caudate lobe and lateral segment of the left hepatic lobe usually develop hyperplasia while the left medial segment and right lobe show atrophic changes. As a tendency, atrophy is expected mainly in alcohol-induced cirrhosis.

One of the first imaging biomarkers for diagnosing cirrhosis was the evaluation of the caudate lobe hyperplasia with the caudate-right lobe ratio (Figure 6-7). This index chose the bifurcation of the main portal vein as a reproducible landmark to divide these lobes. A ratio greater than 0.65 is associated with cirrhosis with an overall accuracy of 66%. The modified caudate-right lobe ratio uses the right portal vein bifurcation to set the lateral boundary, being abnormal an index greater than 0.9. This index is more accurate (74%) for diagnosing cirrhosis and evaluating its clinical severity as significant differences were found among the three Child-Pugh classes (p<.01).

Caudate hypertrophy is also responsible for the right posterior hepatic notch sign, defined as a sharp indentation on the medial posteroinferior liver surface between the caudate and right lobes. The deeper the notch, the more advance the cirrhosis, having this finding a very high positive predictive value.

Another associated findings related with segmental parenchyma atrophy is the widening of the porta hepatitis demonstrated as a prominent fatty space anterior to the main portal vein and the hepatic artery at the hepatic hilum. The enlargement of the pericholecystic space bounded laterally by the edge of the right hepatic lobe, medially by the lateral segment of the left hepatic lobe is known as the expanded gallbladder fossa sign. Again, both signs have a large positive predictive value but much lower sensitivity. The umbilical fissure also widens. Although all these changes must be considered specific for relatively advance cirrhosis, the enlargement of the hilar periportal space has been demonstrated in early cirrhosis.

Most regenerating nodules are small. Macreregenerative nodules rarely exceed 2 cm in diameter and, therefore, larger nodules should be carefully evaluated to exclude dysplasia and carcinogenesis. Large confluent slightly hypovascularized areas of regenerative nodules may be seen mainly close to the interlobar and intersegmental territories.

Regenerative nodules are homogeneous and non-encapsulated hypointense rounded foci on T2W images while they are usually isointense in T1W images. They are surrounding by fine reticular septa, slightly hyperintense in fat suppressed T2W and
STIR images. Markedly hypointense nodules on the in-phase second echo GRE and T2W TSE images are considered siderotic. Some nondysplastic and nontumoral nodules can be hyperintense on the T1W GRE images, do not contained fat (not loosing signal intensity on opposed-phase imaging) and are not arterialized (do not significantly enhance during the hepatic arterial dynamic phase). This high signal intensity in T1W images is multifactorial but mainly related to the intracellular glycogen content (Figure 8).

Cirrhosis is not the only disease associated with morphological changes of the liver. Regeneration and atrophy can also be found in disorders such as Budd-Chiari syndrome, postchemotherapy, regenerative hyperplasia and portal cavernomatosis.

**IMAGING INFLAMMATION AND NECROSIS**

Standard T1W and T2W images are not sensitive to the inflammatory liver changes. On the contrary, respiratory triggered TSE-STIR images depicts an increase in the liver brightness when there is an increase in the water content due to intercellular edema, inflammation or cell necrosis (Figure 11). This increased signal can be qualitatively assessed if the inversion time TI is properly adjusted so that the normal liver signal intensity is quite similar to the signal of paraspinal muscles (150 msec at 1.5 Tesla magnets). In chronic hepatitis and cirrhosis, this increase in the liver signal intensity can be considered a surrogate marker of portal inflammation and periportal and lobulillar necrosis. The liver signal in STIR images is not influenced by the presence of fibrosis or steatosis. However, the presence of iron decrease the liver signal intensity and mask the increased signal of the necroinflammatory infiltrates. If iron is present, the necroinflammatory activity can not be properly estimated with TSE-STIR images.

Reactive lymph nodes at the hepatic hilus and gastrohepatic ligament are also well-known findings. Lymphadenopathy occurred more frequently in autoimmune and virus-induced cirrhosis (Figure 10). Superior diaphragmatic adenopathies are usually hyperplastic, even when an HCC is present. A prominent cisternae chili, with a diameter larger than 2 mm, is observed in uncompensated cirrhosis with a high positive predictive value of 96% due to impairing lymphatic circulation in cirrhosis (verma, abdominal radiol). In patients with portal hypertension, hepatic hilar lymphatics become distended and obstruct the hepatic venules, increasing lymph production in patients with advanced liver diseases and more marked in uncompensated patients.

Dynamic contrast-enhanced MR images may demonstrate in the late arterial phase a heterogeneous pattern of patchy parenchymal enhancement with large geographical areas showing a slight hypovascularization. This frequent finding (50% of cases) of perfusion heterogeneity relates to the presence of inflammatory macrophages, variable hepatocyte necrosis, and increased steatosis. These areas may progress to areas focal confluent fibrosis and collapse.
In the cellular phase after HBCM, a decreased and heterogeneous enhancement relates to the presence of hepatocyte necrosis intermixed with fibrous bands. Areas of regeneration may demonstrate an increased enhancement related to the percentage increase in the number of hepatocytes and impaired bile excretion. In cirrhosis, the severity of the hepatic injury relates to the down-regulation of the HBCM transporter expression. Although a threshold response, with significantly decreased changes appearing in advance stages but not before, Gd-EOB-DTPA hepatic extraction fraction can be considered as a direct, noninvasive technique for the quantitative evaluation of liver function. This extraction ratio is calculated from deconvolution analysis of aortic and hepatic parenchymal time-intensity curves obtained by dynamic MRI and could be a promising alternative for the determination of noninvasive hepatic function in patients with liver disease.

On the T2*W GRE images acquired with a long TE (7 msec.) the less hypointense areas are statistically related to reduction in their functional status. Heterogeneous R2* shortening is also a reliable predictor of advanced fibrosis, with a positive predictive value of 93%. Unfortunately, SPIO measurements are insensitive to early and moderate abnormalities. As mentioned, iron oxide particles will clearly depict the fibrotic bands surrounding the hypointense negatively enhance regenerative nodules.

In a study in patients with liver biopsy, ADC was not correlated with inflammation grades. However, more recent studies have shown a significant relationship between ADC and inflammation scores, being ADC a predictor of inflammation grade 1 or greater. Unfortunately, the ADC values are influenced by the choice of b-value, are multifactorial (steatosis, fibrosis, perfusion) and vary between different vendors, limiting the role of standard ADC calculations.

**IMAGING FIBROSIS**

Routine MR imaging can not observe early fibrosis, but these images are sensitive for detecting moderate and advance fibrosis by demonstrating the reticular pattern of the fibrotic bands surrounding regenerative nodules. This fine reticulation is hyperintense on T2W fat suppression images and on the equilibrium and delayed images after contrast administration. This appearance is due to the coexistence of inflammation in these fibrotic areas. The fine sieve appearance, occasionally associated to poorly defined subcapsular retractile stellate areas, are clear indicators of the presence of advanced fibrosis. Confluent mass like lesions can also be depicted. The observation of this pattern is facilitated by decreasing the signal intensity of the nodules after SPIO administration while increasing the signal from the septa after gadolinium-enhancement (2). This double contrast technique has been shown to be accurate for advance fibrosis. Although this method separates advanced fibrosis or cirrhosis (F3-F4) from intermediate, early or none fibrosis (F2-F0), it does not allow to differentiate no (stage F0), from minimal (stage F1) and intermediate (stage F2) fibrosis.
Areas of focal confluent fibrosis are usually found in long-standing cirrhosis, mainly if associated to alcohol abuse. They are frequently multiple, being the most classical situations the interlobar and intersegmental fissures, as these areas have terminal territory perfusion. The collapse area has a geometrical (often triangular or quadrilateral) capsular-based wedge shape pointing to the hepatic hilum. These peripheral areas of necroinflammatory fibrosis associate volume loss and capsular retraction with focal flattening and even concavity of the adjacent liver surface. The abnormality is moderately hyperintense in T2W images, isointense or slightly hypointense on T1W, with a progressive and delayed enhancement after contrast media administration. Trapped vessels and dilated biliary ducts can be seen within the abnormality. On the cellular phase images after HBCM and SPIO administration the enhancement is usually decreased due to cell necrosis. Internal focal areas of contrast pooling correspond to residual functioning liver parenchyma.

Microscopic water diffusion is decreased in cirrhosis. The reduced liver diffusion can be qualitatively observed on the DW images. Some studies have analyzed the role of DW imaging (Figure 19, 20, 21), mainly thought-out mean ADC comparisons, in the evaluation of chronic diffuse liver diseases. Although ADC values vary with the b-values and motion correction techniques, the ADC values of cirrhotic livers are significantly lower. The shortest ADC values in cirrhosis are mainly related to a decrease in the capillarity perfusion component and not to a true microscopic diffusion restriction associated to fibrosis and inflammation.

Taouli et al. evaluated the DW technique as a predictor of the presence of moderate and advanced liver fibrosis. They analyzed patients with chronic hepatitis versus healthy volunteers by the calculation of the ADC (breath hold, six b-values of 0, 50, 300, 500, 700 and 1,000 s/mm²) found that hepatic ADC was a significant predictor of stage F2 or greater and stage F3 or greater fibrosis. Similar results were obtained by Lewin et al., where DW (navigator-triggered, four b-values: 0, 200, 400, and 800 s/mm²) was compared to other non-invasive methods to conclude that patients with moderate-to-severe fibrosis (F2-F3-F4) had hepatic ADC values lower than those without or with mild fibrosis (F0-F1) and healthy volunteers. In discriminating patients staged F3-F4, the sensitivity, specificity, positive predictive value, and negative predictive value were 87%, 87%, 72%, and 94%, respectively, with an ADC cutoff level of 1.21 x 10^-3 mm²/s.

Luciani et al. analyzed influence of fibrosis in liver diffusion properties by IVIM technique (respiratory triggered, ten b-values: 0, 10, 20, 30, 50, 80, 100, 200, 400, 800 s/mm²; respiratory gated). They observed a restricted diffusion in patients with cirrhosis mainly related to variations in the perfusion component, reflecting decreased perfusion, as well as alterations in pure molecular water diffusion in cirrhotic livers. Confirming this observation, Girometti et al. (breath hold acquisition; six b-values: 0, 150, 250, 400, 600, 800s/mm²,) also concluded that the perfusion component presents a higher accuracy at lower b-values for the assessment of liver fibrosis. The studies in rats with hepatic fibrosis, both in-vivo and immediately after death, also pointed in this direction.
Although IVIM seems to be a promising technique in the diagnosis and staging of fibrosis, some bias must be clearly controlled to standardize this biomarker. The concomitant effect of MR machines, MR sequence parameters, fat, iron, inflammation and necrosis on the ADC values should be evaluated.

Cirrhotic liver vascular perfusion changes are related to the disease activity and staging. Although the arterial blood supply is increased due to the decreased portal flow, the buffer is not sufficient to maintain adequate liver perfusion because of the high level of extrahepatic portosystemic shunting. The overall reduction of the total liver perfusion can be quantified as a prolongation of the mean transit time and a decrease in mean peak liver enhancement.

Another phenomenon is observed as fibrosis development leads to progressive arterializations of the hepatic sinusoidal bed, with shunting and hyperdynamic circulation, and augmentation of the extracellular interstitial space with collagen deposition. These changes produce an overall increased on the liver enhancement during the equilibrium phase images of the dynamic series. Some parametric pixel-by-pixel mapping, such as the mean and maximal enhancement ratios, show significantly higher values than normal livers. An increase in the liver enhancement can be quantified also with the area under the curve and is statistically related to the degree of chronic hepatic insufficiency. A dual-input single compartment model demonstrates an increase distribution volume (related to the increased interstitial volume) and mean transit time (related to the collagen deposition in the extracellular spaces of Disse).

These perfusion modifications can be separately and objectively evaluated through the pharmacokinetic compartment model analyses. Although the experience is limited, cirrhotic livers have an increased vascular permeability ($K^{\text{trans}}$) and extracellular space ($u_e$) with a heterogeneous distribution. These parameters correlate with the grade of liver fibrosis and may be used as a hemodynamic biomarker in injured fibrotic livers (Figures 24, 25).

MR Elastography uses a sound wave generator applied to the patient (Figure 27). The shear mechanical compressional waves are transmitted through the liver, detected with Phase-Contrast sequences, and analyzed (wave propagation and tissue deformation). The calculated elasticity maps show the shear elasticity modulus (kPa) at each point. Quantitative stiffness parametric maps, also known as elastograms, become more heterogeneous with increasing fibrosis. Liver stiffness increases as the stage of fibrosis advances. While the differences in stiffness between patients with early stages of fibrosis (F0 vs. F1 vs. F2) are small with overlap between groups, the differences between higher stages (F2 vs. F3 vs. F4) are large with little overlap.

MR Spectroscopy enables the in vivo noninvasive quantization of some biochemical compounds. Single voxel proton hepatic MR spectroscopy can be obtained with sufficient quality. Glutamine and glutamate complex (Glx), phosphomonoesters (PME), glycogen and glucose complex (Glyu), and lipids are clearly observed. Chronic hepatitis and
cirrhosis showed an increased in Glx, PME, and Glyu levels relative to the lipid content. This increase is related to the severity of fibrosis, although data overlap is present between groups.

**IMAGING VASCULAR CHANGES**

Early fibrosis associates deposition of collagen in the Disse space with alteration of the sinusoidal architecture result in a decreased portal venous flow, which is counteracted by an increase in hepatic arterial flow (buffer response). When venous inflow blockade occurs and vascular resistance increases, the portal flow may be adequate for centrally located parenchyma areas but not for the subcapsular regions. The arterial response may generate enhancement of these peripheral zones with relative hypointensity in the central perihilar areas.

On the contrary, as already mentioned, there may be also a heterogeneous pattern of slight hypervascular behavior within geographical areas due to the presence of necroinflammatory infiltrates and steatosis. Other common causes of perfusion abnormalities to be taken into consideration in cirrhotic livers are related to spontaneous arterioportal shunts, shunts associated to vascular compression (HCC, inflammatory changes, biliary tree dilatation) and portal occlusion.

Portal hypertension frequently complicates liver cirrhosis. Dilatation of the portal vein and its tributaries, with extrahepatic collateral circulation, splenomegaly and ascites are clear signs. Esophageal and gastric varices, paraumbilical, spleno-renal, retroperitoneal and puborectal shunts are well visualized with contrast enhanced MR images and MIP projections. MR images after Gd administration depict esophageal varices in most (81%) cases with a statistically significant relationship with the endoscopy grading of the severity. Vascular engorgement of the mesenteric vessels may produce a pseudoomental cake appearance. Gallbladder wall thickening is associated to venous and lymphatic congestion in the presence of portal hypertension and drainage difficulty.

A relatively small main portal vein in patients with cirrhosis may indicate hepatofugal flow. Even early arterial phase enhancement of the portal vein has been reported as a sign of hepatofugal flow although this finding is misleading as the late arterial phase mixes with the early portal phase.

In most cases, perfusion abnormalities are easy to interpret on the NSCM enhanced images as they have clearly-defined and straight-line margins, corresponding to a vascular territory, and normal vessels coursing through the abnormality. When the portal flow is decreased or absent and the arterial flow volume is increased, they are often seen as hyperarterialization with fading or disappearance in the portal and equilibrium phases.

**IMAGING BILIARY CHANGES**
Liver cirrhosis may result in peribiliary cysts. Cysts abnormalities occur in the peribiliary tissues adjacent to the large intrahepatic and extrahepatic ducts in association with severe liver disease, being usually asymptomatic. These cysts have variable size and morphology and represent cystic dilatation of the extramural glands in the periductal connective tissue. Peribiliary cysts show imaging findings of simple cysts, with low signal intensity on T1W and high signal on heavily T2W MR images.

Primary sclerosing cholangitis show irregular intra- and/or extrahepatic bile duct dilatation and stenosis together with periportal T2W hyperintensity in the major portal tracts. Cirrhosis from advanced PSC develops marked atrophy of the posterior aspect of the right lobe and the lateral segment of the left lobe with hypertrophy of the caudate lobe.

In primary biliary cirrhosis intrahepatic bile ducts are progressively destroyed due to chronic nonsuppurative cholangitis. On T2W images a periportal hyperintensity, especially at earlier stages of disease, may be seen.

**IMAGING FAT**

Cirrhotic livers may have an increase in the fat content. Also, steatosis and nonalcoholic steatohepatitis leads to a fibrosis and cirrhosis. Early detection and follow-up of steatosis would facilitate a better diagnosis and intervention before liver damage is irreversible. A high number of patients with NASH and chronic hepatitis may have also increased iron content in the liver, all these factors affecting the imaging signal characteristics (Figure 31).

Chemical shift T1W dual echo GRE images allow the qualitative diagnosis of steatosis. For the quantitative evaluation, the fat content computed from in-phase and opposed-phase images is erroneous unless a correction is made for the influence of T2* decay. The T2W TSE with and without fat suppression method is easier and accurate enough in clinical settings. However, single voxel proton MR spectroscopy, although limited by the volume sampling, will be needed in clinical trials and longitudinal studies to further increase accuracy.

**IMAGING IRON**

Cirrhosis is frequently associated with an increased deposition of iron, mainly in alcoholic cirrhosis, and iron overload may lead to cirrhosis. Conventional chemical shift dual echo GRE T1W and TSE-STIR images will demonstrate the liver signal intensity drop, allowing the qualitative diagnosis of significant iron deposits. When iron has been demonstrated, a quantitative measurement should be obtained.
Both the liver-to-muscle signal ratio and the liver R2* relaxation rate significantly correlates with the amount of iron content (Figure 32). Although sequences and postprocessing of images for T2 and T2* relaxation rates calculations are more difficult to implement in a clinical environment, this approach must be preferred to the simple signal ratio determination in clinical trials. The calibration between R2* and iron concentration is dependant on field strength, being different for 1.5 and 3 Tesla magnets.

The coupling of multiecho GRE techniques with chemical shift imaging may simultaneously evaluate both iron and fat liver content. This is relevant as both entities may simultaneously coexist in a significant number of cases with chronic liver disease.

**IMAGING NEOPLASIA**

Any liver imaging evaluation in cirrhotic patients should also search for tumor development. Overt HCC are characterized by a mass lesion showing hyperarterialization with wash-out, becoming hypointense to the liver on the delayed phases after contrast administration. The presence of a capsule and internal mosaic appearance are secondary criteria. Dysplasia, atypia and early neoplasic degeneration is much more difficult to demonstrate. In this setting, any hyperintensity within a nodule in the T2W images and hyperintense nodules in the T1W images may be considered suspicious and their perfusion characteristics carefully evaluated. DW images may help in clarifying a malignant transformation is a clear diffusion restriction is observed.

Some special situations in cirrhotic livers need further comments. Nodular appearance of an arterioporal shunts is typically seen in cirrhosis as a small and non-encapsulated area with ill-defined margins. They are not seen on the plain non-contrast enhanced images, delayed equilibrium and cellular phases after HBCM and RECM, allowing the differentiation with small HCC.

To differentiate a nodular arterioportal shunt from a small HCC without wash-out on the equilibrium phase images, specific contrast media (either HBCM or SPIO) can be useful if no significantly different uptake is seen, a finding typical of arterioportal shunts. A transient hepatic arterialization may highlight a small HCC determining portal compression. This is also the situation with peribiliary transient hepatic arterialization caused by long-standing biliary obstruction.
Assessment of diffuse liver disease (including cirrhosis)

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Fig. 0: Figure 1

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Learning Objectives:

- To learn the imaging features of cirrhotic diffuse liver disease.
- To learn the imaging features of non-cirrhotic diffuse liver disease.
- To learn how imaging can help in the quantification and follow-up of diffuse liver disease.

Fig. 0: Figure 2

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Why cirrhosis?

- Regeneration
- Inflammation and Necrosis
- Fibrosis
- Vascular changes
- Steatosis
- Iron
- Neoplasia

To be clinically useful, any method used to evaluate chronic hepatitis and cirrhosis must accurately identify regeneration, inflammation, necrosis, fibrosis, fat, iron and also neoplasia. Fibrosis, necroinflammatory activity, fat and iron deposits are the most important parameter for antiviral treatment indication and follow-up.

Fig. 0: Figure 3

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Cirrhosis

Cirrhosis is a diffuse abnormality of the liver architecture caused by fibrosis and regenerating nodules with a 5 year survival rate is 90%.

Chronic and irreversible, it is the final stage of different processes, mainly caused by alcohol, viruses, hemochromatosis and non-alcoholic steatohepatitis.

HCC development rate: 8% at 5 years, 25% at 10 years; independently of the antiviral treatment.

Although liver biopsy is a relatively safe procedure when performed by experienced clinicians, it has poor patient acceptance, is not risk free, and is difficult to repeat. In addition, liver biopsy is prone to interobserver variability and sampling errors, and is more expensive than MR imaging.
### Why MRI?

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**Fig. 0:** Figure 5

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**Imaging regeneration**

**Caudate-Right Lobe Ratio**

- Line 1 is drawn through the right lateral wall of the bifurcation of the right portal vein.
- Line 2 is drawn through the most medial margin of the caudate lobe.
- Line 3 is drawn perpendicular and midway between the main portal vein and inferior vena cava.
- Distance C’ is the width of the caudate lobe and distance R’ is the width of the right lobe.
- CRI > 0.9.

*Fig. 0: Figure 6*

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Imaging regeneration

Global or segmental volumetric changes associated with regional variations in the portal venous blood supply.

- Caudate lobe and left lateral segment hyperplasia.
- Right posterior hepatic notch sign (caudate and right lobe boundary). The deeper the notch, the more advance the cirrhosis.
- Caudate lobe hyperplasia (caudate-portal index > 0.6).

Fig. 0: Figure 7

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Imaging regeneration

Chronic hepatitis does not modify the macroscopic architecture of the liver

Cirrhosis generates typical morphologic changes in the liver parenchyma and surface contour by changing the liver architecture due to regenerating nodules, necrosis and fibrous development:

- Fine and diffuse surface nodularity, more prominent on the hypertrophied segments.
- Regenerating nodules may be seen as a small mosaic liver pattern.

Fig. 0: Figure 8

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MR in Hepatology

What do we know?

- Morphologic changes: High resolution MR images
- Necrosis - inflammation - edema: STIR images
- Fat deposits: Chemical shift T1W-GE images
- Iron overload: Quantification with T2*W-GE images
- Gd-enhanced Perfusion: Arterial, Portal & Interstitial phases
- Cellular functionality: Organ-specific contrast agents

**Fig. 0:** Figure 9

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Reactive lymph nodes at the hepatic hilus and gastrohepatic ligament.

Lymphadenopathy occurred more frequently in autoimmune and virus-induced cirrhosis.

Diffuse hypercellular hematopoietic marrow hyperplasia (marrow reconversion).

Fig. 0: Figure 10

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STIR liver signal intensity can be considered a surrogate marker of inflammation and necrosis.


**Fig. 0:** Figure 11

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- Standard T1W and T2W images are not sensitive to necro-inflammatory changes.
- In STIR images the signal of the normal liver is similar to fat and slightly higher than the paraspinal muscle (TI ≈ 150-160 ms at 1.5 T and 170-180 at 3.0 T).
- The variations in the liver brightness are mainly related to water (intracellular edema, inflammation, cell necrosis).

Fig. 0: Figure 12

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Imaging vascular changes

- CE-DMR with MIP: Dilatation of the portal vein and its tributaries, with extrahepatic collateral circulation, splenomegaly and ascites.
- MR shows esophageal varices in 81% of cases.
- There is a statistically significant relation between MR and endoscopy grading of the severity (p < 0.05).

Fig. 0: Figure 13

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Imaging regeneration

Regenerative nodules are homogeneous and non-encapsulated hypointense rounded foci on T2W images, surrounding by fine reticular septa, slightly hyperintense in fat suppressed T2W and STIR images.

Hypointense nodules on the in-phase second echo GRE and T2W TSE images are considered siderotic.

Some nondysplastic and nontumoral nodules can be slightly hyperintense on the T1W GRE images.

Fig. 0: Figure 14

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Imaging regeneration

- Widening of the porta hepatis: prominent fatty space anterior to the main portal vein and the hepatic artery at the hepatic hilum.

- Enlargement of the pericholecystic space or expanded gallbladder fossa sign.

**Fig. 0**: Figure 15

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Liver enhancement after extracellular contrast media administration is related to the degree of inflammation, necrosis and fibrosis.

Dynamic CE-MR images may demonstrate in the late arterial phase a heterogeneous pattern of patchy parenchymal enhancement with large geographical areas showing a slight hypovascularization.

**Fig. 0:** Figure 16

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Imaging Inflammation - Necrosis

In the cellular phase after HBCM, a decreased and heterogeneous enhancement relates to the presence of hepatocyte necrosis intermixed with fibrous bands.

Areas of regeneration may demonstrate an increased enhancement related to the percentage increase in the number of hepatocytes and impaired bile excretion.

In cirrhosis, the severity of the hepatic injury relates to the down-regulation of the HBCM transporter expression.

Fig. 0: Figure 17

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Fig. 0: Figure 18

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Fig. 0: Figure 19

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Imaging Fibrosis and Perfusion

The biexponential modeling of the signal decay (IVIM).

\[ S_I = S_0 \cdot f \cdot e^{-b \cdot D^*} + S_0 \cdot (1 - f) \cdot e^{-b \cdot D} \]

\( f \): vascular volume fraction (\%)  
\( D^* \): Perfusion component  
\( D \): Diffusion component

**Fig. 0:** Figure 20

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Fig. 0: Figure 21

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Decreased ADC correlated with increased liver fibrosis, but not after death.

Restricted diffusion in fibrosis must be explained by a decrease of perfusion in vivo in rats with liver fibrosis.

**Fig. 0:** Figure 22

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**Imaging Fibrosis**

- Microscopic water random displacement
- Fibrosis in cirrhosis decreases the ADC.

ROC curves with ADC for prediction of stage 2 or greater (left) and stage 3 or greater (right) hepatic fibrosis (b values of 0, 50, 300, 500, 700, and 1,000 s/mm²).

*Fig. 0:* Figure 23

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Imaging Fibrosis

- Significant decreased venous permeability ($K_{trans_2}$) in cirrhotic patients ($197.8 \pm 89.3$ vs. $298.3 \pm 52.8$, p<0.02).

- Trend towards higher arterial permeability ($K_{trans1}$) in cirrhotic patients ($74.5 \pm 62.9$ vs. $48.8 \pm 39.4$, p=0.363).

$K_{trans}$ arterial

$V_e$

$K_{trans}$ portal


**Fig. 0**: Figure 24

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**Imaging Fibrosis**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Units</th>
<th>Full name</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{\text{trans}}$</td>
<td>min$^{-1}$</td>
<td>Volume transfer constant between blood plasma and Extravascular Extracellular Space</td>
</tr>
<tr>
<td>$V_e$</td>
<td>-</td>
<td>Interchangeable Volume of Extravascular Extracellular Space per unit volume of tissue</td>
</tr>
<tr>
<td>$K_{\text{ep}}$</td>
<td>min$^{-1}$</td>
<td>$K_{\text{trans/ve}}$, Rate constant between Extravascular Extracellular Space and blood plasma</td>
</tr>
</tbody>
</table>

\[ C_z(t) = \int_0^t \left( k_{\text{at}} C_a(x) + k_{\text{pt}} C_p(x - \tau) \right) e^{k_{\text{pe}}x} dx \]

- Fibrosis may be also responsible for pharmacokinetic changes:
  - Decreases vascular flow (arterial and portal)
  - Increases delayed ECS enhancement (KHO)

**Fig. 0:** Figure 25

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Fig. 0: Figure 26

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Imaging Fibrosis

MR is sensitive for detecting moderate and advance fibrosis by demonstrating the reticular pattern of the fibrotic bands surrounding regenerative nodules.

This fine reticulation is hyperintense on T2W fat suppression images and on the equilibrium and delayed images after contrast administration.

Associated to poorly defined subcapsular retractile stellate areas.

Fig. 0: Figure 27

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Imaging Fibrosis

- Double contrast-enhanced MR (SPIO and Gd) with sGRE-T1W (TE 4.7 msec @ 3 minutes after Gd administration).
- Heterogeneous R2* shortening is a reliable predictor of advance fibrosis, with a PPV of 93%.
- SPIO will clearly depict the fibrotic bands surrounding the hypointense negatively enhance regenerative nodules. Fibrotic areas with necrosis are hyperintense in T2*W images due to lack of enhancement.
- Texture analysis differentiates ≥ F3 vs. ≤ F2 (p < 0.001).
- Hyperintense reticulation and hypointense nodularity accuracy is higher than 90%.

Fig. 0: Figure 28

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Imaging Fibrosis

Liver ex vivo and in vivo MR Spectroscopy with SV (TE 136 ms).

Fig. 0: Figure 29

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On T2*W GRE images after SPIO administration, the less hypointense areas are statistically related to reduction in their functional status.

**Fig. 0:** Figure 30

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**Imaging Steatosis**

Turbo Spin Echo Fat Suppression signal decay

\[
\frac{(SI_{T2-2} - SI_{T2FS})}{SI_{T2}} \cdot 100
\]

**Fig. 0:** Figure 31

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TSE: high signal of fat (J coupling) and insensitivity to iron
**R2* Maps**

There is a strong correlation between T2* and iron concentration, although water (inflammation) may be a confounding factor.

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**Fig. 0:** Figure 32

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Fig. 0: Figure 33

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