ROLE OF COMPUTED TOMOGRAPHY IN THE EVALUATION OF THE PATIENTS WITH HEPATITIS C-RELATED LIVER CIRRHOSIS

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ROLE OF COMPUTED TOMOGRAPHY IN THE EVALUATION OF THE PATIENT WITH HEPATITIS C-RELATED LIVER CIRRHOSIS (Abstract): Cirrhosis is an increasing cause of morbidity and mortality, one of the most common causes being hepatitis C virus (HCV) infection. Diagnosis, staging and complication assessment are equally important in patients’ management, as well as establishing the right indication for antiviral treatment and further follow-up. So far, it is well recognized the role of multidetector computed tomography (MDCT) in the evaluation of focal liver lesions in the cirrhotic liver, while its capabilities of describing morphological changes of the liver and the extrahepatic response to increased portal pressure is less extensively used. The aim of this review is to underline the utility of MDCT as a useful complementary tool in the evaluation of patients with hepatitis C-related cirrhosis. Keywords: CIRRHOSIS, HEPATITIS C VIRUS, COMPUTED TOMOGRAPHY, HEPATOCELLULAR CARCINOMA, MORPHOLOGICAL CHANGES OF LIVER.

Cirrhosis is the final stage of chronic liver diseases. Even if there are many possible causes of chronic liver injury, the histological pathway is similar, characterized by fibrosis and change of normal liver structure into a distorted architecture consisting in regeneration nodules. Moreover, there is vascular remodeling, which results in the formation of intrahepatic shunts of the arterial and portal vessels into the central vein and impairment of the exchange between liver parenchyma and sinusoids (1).

In the more developed countries, the main causes of cirrhosis are: hepatitis C virus (HCV) infection - the leading cause of liver-related morbidity and mortality worldwide (2), alcoholic liver disease, non-alcoholic fatty liver diseases, hepatitis B virus, and others (the most common being autoimmune hepatitis, hereditary liver diseases, drug-induced liver disease) (3, 4). A recent study covering the geographic area of Europe has estimated that the prevalence of HCV ranges from 2.4% in Western and Central Europe to 2.9% for Eastern Europe (5). The risk and progression of fibrosis associated with HCV have been correlated with host factor rather than viral factor: there is no relationship between viral load and genotype and the severity of fibrosis, the human promoter polymorphism appears to correlate with fibrosis and host immune phenotype may be critical, with more rapid progression in
imnosuppressed patients (6).

In the present days, interferon (IFN)-free treatment represents the paradigm for treatment of chronic hepatitis C with high rates of sustained virologic response (SVR). Several recent and ongoing studies show that IFN-free regimens using direct-acting antiviral (DAA) combinations can cure most chronically infected HCV patients (7).

The progression of liver fibrosis is not a continuous process but rather has a non-linear course depending of various factors like sex, age, alcohol consumption and obesity. The former gold standard liver biopsy is currently considered insufficient for frequent monitoring because of its disadvantages: it is expensive, may have complications and its accuracy suffers from sampling variation. The ideal noninvasive liver fibrosis assessment should be simple, accurate, inexpensive and widely available (8). The new noninvasive methods in use today have two different but complementary approaches: the biological approach based on the quantification of biomarkers in serum samples and the physical approach based on the stiffness of liver parenchyma, a more specific marker (9). Liver stiffness is measured by using transient elastography, acoustic radiation force impulse imaging (ARFI) and magnetic resonance (MR) elastography. These noninvasive methods are widely used and have equal advantages and limitations. Serum tests are not specific to the liver, unable to discriminate between intermediate stages of cirrhosis, and the results are not immediately available. Transient elastography requires a dedicated device and region of interest cannot be chosen, has low applicability in obesity and ascites. MR elastography is time-consuming and costly, and is not applicable in iron load (9, 10).

CT has been considered insufficient as a non-invasive method of staging fibrosis in comparison with ultrasound elastography and laboratory testing, or magnetic resonance (11). Along with the advantages of being a widely used, reliable and affordable examination, nowadays there is some progress in new approach techniques that may promise the utility of CT in the detection and precise staging of fibrosis.

The main use of CT examination is the detection of hepatocellular carcinoma (HCC), the most fearsome complication, especially in patients with high serum α-fetoprotein levels, which are at the highest risk. Also, there are some concerns related to the higher incidence of HCC following IFN-free antiviral therapy, most likely a consequence of the removal of the upregulated inflammatory status as a control mechanism of the new malignant cell growth (12).

The aim of this article is to illustrate the main aspects of the pathological process as they appear on CT examination, underline the morphological transformation of the liver in volume and shape, the structural and textural changes.

Liver assessment

Morphological changes in the liver vary with the stage of fibrosis. Hepatomegaly is the early sign in more than 60% of patients (13). As the disease progresses there is an architectural change and, due to the alteration in portal blood flow, one theory suggests that the blood does not mix well and "streams" do occur (14). The right lobe receives most of its blood from the superior mesenteric vein so it is more exposed to toxins and the consequence is the atrophy
of the right lobe posterior segments (VI and VII) and medial segment of the left lobe (IV). On the other side, the left lobe receives blood from the splenic vein and is more exposed to the pancreatic hormones that promote hypertrophy, so there will be an enlargement of the lateral segments of the left lobe (II and III). Caudate lobe enlargement is due to the supply of left branches or bifurcation of portal vein, and because the flow is increased by the shorter intrahepatic course of the branches (15).

The typical appearance of the cirrhotic liver on CT is transversal enlargement of lateral segments and atrophy of the medial segment of the left lobe and atrophy of the posterior segments of right lobe and hypertrophy of the caudate lobe (fig. 1).

An important consequence of this liver remodeling is the presence of right hepatic notch sign defined as a sharp indentation developed between the caudate and right lobe of the liver (fig. 2). The presence of hepatic notch is a qualitative method for assessing the hypertrophy of the caudate lobe and atrophy of the right lobe (16).

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**Fig. 1.** Volume rendering image (A) and axial section (B). Typical appearance of the cirrhotic liver: enlargement of the lateral segment of the left lobe and atrophy of the medial segment with classical “tongue-like” appearance of the left lobe, enlargement of the caudate lobe and shrinking of the posterior segments of the right lobe.

**Fig. 2.** (A) The posterior - inferior surface of the right hepatic lobe at the level of the right kidney is normally concave owing to the renal impression (white arrows) (B) In patients with cirrhosis a sharp indentation develops between the caudate and the right lobe of the liver.
Other morphological changes seen in cirrhosis are: blunt liver margins, widening of the periportal space, expansion of the pericolecystic space and enlargement of the interlobar fissure (17).

Widening of the periportal space is a consequence of segment IV atrophy. Although the exact mechanism remains unclear, it is believed to be related to portal vein hypoperfusion. An enlarged hilar periportal space, defined as a distance between the right portal vein and the posterior edge of segment IV greater than 10 mm, may be the only morphological sign in earlier stages of cirrhosis.

In normal liver, the gallbladder fossa is delimitated laterally by the right lobe and medially by segment IV, and contains little fat. In cirrhotic liver, the gallbladder fossa can be enlarged. The expanded gallbladder fossa in cirrhosis may be the consequence of four factors: atrophy of the medial segment of the left hepatic lobe and hypertrophy of the caudate lobe, atrophy of the anterior segment of the right hepatic lobe with counterclockwise rotation of the major interlobar fissure and enlargement in the cephalocaudal direction of the left hepatic lobe (13, 18).

Hypertrophy of the caudate lobe and atrophy of the right lobe were at the basis of the attempts to stage fibrosis. There are few studies investigating the accuracy of CT findings in liver fibrosis: In 1980 Harbin et al. (19) developed a cirrhosis score using the ratio of the width of the transverse caudate lobe to the width of the transverse right lobe, a ratio > 0.65 is 96% and > 0.73 is 99% likely to be cirrhotic (fig. 3). Because the hypertrophied caudate lobe extended beyond the main portal vein bifurcation, in 2002 Awaya et al. (15) used a modified version of this ratio with much more sensitivity using the bifurcation of the right portal vein as a landmark.

![Fig. 3.](image)

(A) Harbin method image: axial slice immediately below the bifurcation of the main portal vein line 1: parasagittal line drawn through the right lateral border of the portal vein, line 2: parasagittal line drawn through the left lateral border of the caudate lobe, line 3: line orthogonal to lines 1 and 2 midways between the portal vein and the IVC extended to the right liver edge. RL measurement: along line 3, from right liver edge to line 1. C measurement: along line 3, between line 1 and line 2. Caudate-right lobe ratio: C/RL.

(B) Hypertrophied caudate lobe extended beyond the main portal vein bifurcation and modified C/RL uses the bifurcation of the right portal vein as a landmark.

A ratio greater than 0.55 suggested a diagnosis of cirrhosis.
The latest attempt was in 2014, when Huber et al. (20) used the sum diameters of the hepatic vein divided by modified caudate - right lobe ratio with a sensitivity of 83% and a specificity of 76% for precirrhotic liver fibrosis, and a sensitivity of 88% and a specificity of 82% for cirrhotic liver fibrosis (fig. 4).

**Fig. 4.** Patient with right hepatic vein smaller than 9 mm, the ratio of the sum of hepatic vein divided by the modified caudate-right hepatic lobe diameter is 8.9, and is suggestive for cirrhosis.

**Contour and texture changes**

Diffuse fibrosis is the main cause of heterogeneity of the liver. It is better seen on unenhanced CT and may have four different patterns of distribution: poorly defined region of low attenuation, thin perilobular bands of low attenuation, thick bridging bands of low attenuation, and diffuse fibrosis causing perilobular cuffing (21) (fig. 5).

**Fig. 5.** Different patterns of diffuse fibrosis are seen on CT: (A) Patchy, poorly defined region of low attenuation, (B) Thin perilobular bands of low attenuation, (C) Thick bridging bands of low attenuation (D) Diffuse fibrosis with perilobular cuffing.

Surface nodularity is a direct consequence of the presence of regenerative nodule. The liver contour may be smooth, nodular, fine to coarse if they are < 3 cm,
or grossly lobular if they are more than 3 cm diameter (22) (fig. 6). This direct relationship between hepatic distortion and the surface embossing may predict the underlying hepatic fibrosis.

Recent studies tried to use liver surface nodularity as a biomarker to allow CT examination alone to accurately discriminate between stages of liver fibrosis comparable to elastography (23, 24). Moreover, a multiparametric analysis is possible in the near future, using a combination between the liver surface nodularity quantification and other CT biomarkers that are already available, like the volumetric and textural features (24).

The diagnosis of liver cirrhosis based on selected independent variables, such as irregular and nodular surface, parenchymal abnormalities, morphological changes, and manifestation of portal hypertension has in one study by Kudo et al (25) an accuracy of 71.9%, sensitivity of 77.1% and specificity of 67.5%.

![Fig. 6. Fine nodularity of liver contour, (left image) “cobblestone” margin (right image).](image)

**Regenerative nodules, dysplastic nodules, and hepatocellular carcinoma**

Regenerative nodules (RNs) are defined as an area of liver parenchyma enlarged in response to necrosis and altered circulation or other stimuli, and are surrounded by fibrous septae. According to size, RNs are micronodules if they have less than 3 mm, or macro nodules if they are equal or more than 3 mm. If greater than 15 mm they may harbor dysplastic or malignant foci (26). RNs are present in all cirrhotic livers, but they are revealed in only 25% of unenhanced CT scans. Nodules are difficult to detect on CT because they are too small and like the surrounding tissue (fig. 7). They are detectable when surrounded by hypodense fibrotic bands or when they accumulate iron (siderotic nodules) (21).

A dysplastic nodule (DN) is defined as a nodular region of dysplastic hepatocytes of at least 1 mm in diameter without histologic features of malignancy. DNs are considered an intermediate stage in the progression to hepatocellular carcinoma. They are classified according to histological atypia into low-grade dysplastic nodules, which are composed of hepatocytes that are minimally abnormal, and high-grade dysplastic nodules which have any of the features of low-grade nodules but in addition have one or more of the following: high nuclear-cytoplasmic ratio, irregular nuclear contour, nuclear hyperchromatic, rare mitotic figures, pseudo-gland formation, cytoplasmic basophilia, and resistance to iron accumulation (27).
Role of computed tomography in the evaluation of the patients with hepatitis C-related liver cirrhosis

The prevalence of DNs in patients with cirrhosis ranges from 14% to 37%, but they are not easily distinguishable from the regenerative nodules in the surrounding liver (28). Most of DNs are undetectable by CT. Occasionally there may be a slightly hyperattenuating nodule on non-enhanced scan but without postcontrast enhancement. Tumor angiogenesis seems to be a required step in the progression from regenerative nodule to dysplastic nodule (low-grade to high-grade) and, finally to HCC. During this process, there is a conversion of the vascular supply with an increase in the arterial and decrease in the portal supply. The less differentiated nodules enhance more on postcontrast in early arterial phase and may mimic HCC on CT scan.

HCV promotes carcinogenesis having a direct and indirect role, especially due to fibrosis. In this situation, the chromosomal alteration that occurs in fibrotic tissue is associated with tumor genesis. Another way to promote carcinogenesis is through chronic inflammation of the liver which has been associated with a shift in signaling from tumor suppression to fibrosis and carcinogenesis (29).

HCC is a malignant neoplasm composed of cells with hepatocellular differentiation and is histologically classified as trabecular, pseudo glandular, compact and scirrhous. The most common is the trabecular type. The classical CT features of the HCC are a solitary nodule on non-enhanced scan, often inhomogeneous due to necrosis. Almost all HCCs are highly vascular lesions and exhibit intense contrast enhancement during the arterial phase. Due to the alteration in vascular supply with an increased arterial and decreased portal blood supply, they exhibit washout in the portal phase. Another important CT finding is the presence of the fibrous capsule which is usually enhanced on delayed equilibrium phase images.

Another less common appearance is as an infiltrating mass, a multicentric lesion (mass with daughter lesions) or multifocal lesion (may mimic metastasis).

Liver Imaging Reporting and Data System (LI-RADS) was created by the American College of Radiology and is both a set of standardized terminologies and a classification system for imaging findings in liver lesions. The classification system is meant to be used in livers which have risks factor for HCC. The most suitable are the patients with liver cirrhosis, especially those with HCV infection who are at the greatest risk.

The latest version in use is ver. 2014 applicable to CT and MR and for contrast enhanced ultrasound (CEUS LI-RADS). The advantages of the method are the decrease in error of interpretation by applying the consistent terminology and enabling the communication with the clinician and increased therapeutic performance.

The “observation” is the preferred term for the CT findings which is described using major criteria and ancillary features. Major criteria are: hepatic phase enhancement, washout, capsule, or pseudo capsule and threshold growth. For each of these we have a binary categorization: present or not present. In the dubitative situation, the ancillary features mainly on MR evaluation which may favor malignancy or benignity are used. If assignment is unclear, ancillary findings may be used as “tie-breaker”. The LI-RADS scores range from L-1 which favor benignity to L-5 which favor malignancy (30, 31).

The first two categories are LR-1 benign
and LR-2 probably benign. Such lesions as cysts, hemangioma, vascular anomaly, perfusion alteration, hypertrophic pseudo mass, confluent hepatic fibrosis, focal scar, and lesions which disappear at follow-up without treatment are LR-1. Lesions which have an atypical appearance of the benign entities and cirrhosis-associated nodules are categorized as LR -2.

Observations that are neither definitely or probably benign are categorized based on their diameter and the following features: washout, capsule, or threshold growth in one of the category.

The intermediate probability for HCC is assigned as LR-3 observation, which has a moderate probability of both benign entity and HCC (fig. 8).

LR-4 category is assigned when the imaging features are suggestive, but not diagnostic, of HCC (fig. 9).

LR-5 category is assigned only when there is 100% certainty that the observation is HCC or is proven to be HCC at histology. LR-5V category is assigned when there is definite enhancing soft tissue in a vein irrespective of the presence or absence of visible intraparenchymal HCC. Finally, LR-M is a special category assigned to observations that are probably malignant but not specific for HCC, like metastasis, lymphoma, cholangiocarcinoma (fig. 10).

Fig. 7. (A) Regenerative nodules (arrow) surrounded by lower attenuation fibrosis, (B) High-attenuation nodule (arrowhead).

Fig. 8. LR-3 observation. Liver nodule (< 20 mm) isoattenuation to the surrounding liver in arterial phase, and hypoattenuating in the portal and equilibrium phase (washout).
Fig. 9. LR-4 observation. First row: 17-mm nodule with partial hyperenhancement in arterial phase and capsule in delayed phase; Second row: nodule with partial hyperenhancement in arterial phase and hypo enhancement in venous and delayed phase (washout) but without capsule in delayed phase.

Fig. 10. LR-5 observation (first row) - a large subcapsular mass with arterial hyperenhancement, washout and capsule in delayed phase. LR-5V (second row) - enhanced tumor tissue into right portal vein. LR-M (bottom row) - mass with dynamic enhancement suggestive for cholangiocarcinoma. Note the dilated bile ducts in the left liver lobe.
Repercussion on the extrahepatic abdominal organs in cirrhosis

Extrahepatic abnormalities associated with cirrhosis are mainly a consequence of portal hypertension defined as a pressure greater than 5-10 mm Hg. As the pressure in the portal system increases due to the distortion of the hepatic vasculature and fibrosis, the blood flow is shunted away from the liver to the low pressure systemic vessels and the portosystemic collaterals develop.

The main abdominal manifestations are dilated portal vein, varices, splenomegaly, ascites and bowel wall and mesenteric edema.

Varices appear as a serpentine or tubular structure that enhance after contrast administration. They are located most frequently in the wall of the esophagus and appear as a nodular intraluminal protrusion. Gastroesophageal bleeding is the most common clinical presentation. Another frequent location is in lesser omentum from the left gastric collaterals present in 80% of the patients. Varices can occur on the collateral paraumbilical vessel which communicates with the vessel located in the subcutaneous abdominal wall and reassembling a radial distribution called caput medusae. Portosystemic shunts commonly involve the gastrorenal and splenorenal systems (fig. 11). Nonmalignant portal vein thrombosis may occur in cirrhotic patients and is correlated with the severity of liver disease (32).

Splenomegaly is a result of portal congestion, tissue hyperplasia, and fibrosis. There is a vicious circle: the enlarged spleen requires an increased blood flow which perpetuates the underlying portal hypertension (33).

The exact pathophysiologic mechanism leading to edema of the gallbladder wall is due to a combination of factors: elevated portal venous pressure, elevated systemic venous pressure, and decreased intravascular osmotic pressure. In cirrhotic patients, the gallbladder wall is often thickened measuring more than 5 mm and hypodense (fig. 11).

![Fig. 11. CT appearances of esophageal varices. Intraluminal protrusion with scalloped margins (arrows) (A). Paraesophageal varices (white double arrows) appear as well defined, round, tubular, or serpentine structures situated outside the wall of the esophagus in the mediastinum (B). Dilated paraumbilical veins (C) anterior to the left hepatic lobe (black arrows) arising from the left portal vein (white arrow). Abdominal wall varices radiating from the umbilicus. Connection with inferior epigastric veins (F) and multiple vessels forming caput medusae (E). Thickened gallbladder wall (D). Small bowel wall thickening in a patient with hepatic cirrhosis. CT images show diffuse thickening of the small bowel and colon wall and folds (arrows). Ascites (G) and mesenteric edema (arrowheads) are noted (H).]
Ascites develops when the portal venous pressure exceeds 12 mmHg and is due to increased intravascular hydrostatic pressure and decrease in oncotic pressure. Ascites is visible as a large fluid accumulation into the peritoneal cavity with central displacement of the small bowel and mesentery.

Gastrointestinal wall thickening is mainly caused by edema and has a multisegmental distribution. The jejunum and ascending colon are most often involved and the haustral thickening of the colon is more common than wall thickening. The involvement of other digestive segments such as the duodenum, jejunum, or transverse colon without involvement of the jejunum or ascending colon may have a non-cirrhotic cause like inflammatory, ischemic, and neoplastic disease. Such CT findings should determine the search for another coexisting cause of thickening (34).

Diffuse intra- and retroperitoneal edema may have multiple causes but the most obvious mechanism is portal hypertension which causes increased hydrostatic pressure in the mesenteric vessel and extravasation of the fluid into the mesentery. Often, mesenteric edema is mild and focal and it becomes more diffuse as its severity increases. Presence of omental and retroperitoneal edema are signs of severity and correlates with other findings like severe ascites, subcutaneous edema or pleural effusion (35).

CONCLUSIONS

In our opinion, there is a need for an imaging tool able to monitor the cirrhotic patient, especially after antiviral treatment, and CT might be this tool. CT has been considered inferior to other methods (such as Fibroscan®, serum test and MR) for the noninvasive diagnosis of liver fibrosis, but is fast, widely accessible, and affordable and now there are perspectives in new applications available in the last years, such as contour or texture analysis, and perhaps a combined analysis will provide a more accurate staging of fibrosis.

Moreover, besides the reasonable assessment of fibrosis, CT provides a complete assessment of the liver including the architectural and structural changes such as the vascular and biliary tract changes, and focal and diffuse lesion assessment. For the patients with sustained virologic response it is necessary to redefine a new semiology related to liver remodeling due to regression of fibrosis.

In patients responsive to antiviral therapy, there is a need for more elaborated techniques for the prediction and detection of hepatocellular carcinoma, especially in the context of liver remodeling.

Taking into consideration these advantages, we strongly believe that CT examination provides valuable insights into the extent of the hepatic injuries of cirrhosis and extrahepatic abdominal complication due to portal hypertension and should be used.

REFERENCES

Role of computed tomography in the evaluation of the patients with hepatitis C-related liver cirrhosis


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**NEWS**

**OBSTETRIC AND PERINATAL OUTCOMES OF SINGLETONS AFTER SINGLE BLASTOCYST TRANSFER: IS THERE ANY DIFFERENCE ACCORDING TO BLASTOCYST MORPHOLOGY?**

A strong correlation between blastocyst morphology and morpho kinetics parameters and implantation has been shown by recent studies. The consequences and effects of assisted reproductive techniques on children's short and long-term health have major impact on the subject and focus on reproduction. The obstetric and perinatal outcome of singletons according to blastocyst morphology has rarely been evaluated. The aim of this observational study is to determine whether a relationship exists between blastocyst morphology and obstetric and perinatal outcomes. A total of 799 singleton clinical pregnancies were analyzed after transfer of a single fresh blastocyst - (day 5) between 2006 and 2013. Blastocysts were divided into four groups based on their morphology on day 5: group 1 = good morphology blastocysts; group 2 = fair morphology blastocysts; group 3 = poor morphology blastocysts and group 4 = early (B1/B2) blastocysts. Obstetric and perinatal outcomes were compared between the four groups of this study. Some confounding variables were adjusted but main obstetric and perinatal outcomes after transfer of blastocysts with poor morphological characteristics were not associated with increased adverse obstetric and perinatal events. Sex ratio was significantly higher in group 1 compared with groups 2, 3 and 4, and in Group 2 compared with Group 3 ($P < 0.001$) even after adjustment ($P < 0.05$ ) (Céline Bouillon, Noémie Celton I, Sandra Kassem, Cynthia Frapsauce, Fabrice Guérif. Obstetric and perinatal outcomes of singletons after single blastocyst transfer: is there any difference according to blastocyst morphology? *Reprod BioMed Online* 2017; 35(2): 197-207.

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