Role of MRI in Evaluation of Spectrum of Liver Lesions in Cirrhotic Patients

Anagha Joshi¹, Sukhada Kulkarni²*, Ankita Shah²

Abstract
MRI provides better intrinsic soft-tissue contrast with more enhanced depiction of even subtly different tissue properties making lesion evaluation easy. Faster sequences which capture arterial sequences better, lack of ionizing radiation and simultaneous evaluation of background liver parenchyma and the liver lesions are additional advantages of using MRI as the imaging technique of choice. Comprehensive liver imaging using MRI now includes T1, T2-weighted imaging and in- and opposed-phase, in addition to dynamic post-contrast imaging with proper breath holding techniques. Wider variety of liver specific contrast agents is available for use in MR imaging with the gadolinium based agents being considered the most useful and practical, particularly for lesion characterization.

Aims and Objectives: To evaluate MRI spectrum of liver lesions in cirrhotic patients, Role of MRI in focal liver lesion evaluation and to differentiate benign versus malignant lesions.

Materials and Methods: A prospective study of OPD or IPD patients who underwent imaging tests like Ultrasonography, or CT scan for suspected chronic liver disease was done. A total 35 patients were investigated (July 2014 - November 2016) with MRI abdomen done with the patient in supine position on a Philips Achieva 3.0T MRI scanner. Standard MRI abdomen protocol, including T2W TSE in axial and coronal plane, T2W fat suppressed (SPAIR) images in axial and coronal plane, T1W TFE, in- and out-of-phase imaging and Diffusion-weighted imaging (DWI) in axial plane along with pre-contrast baseline fat-suppressed T1W imaging in at least one plane was acquired. Breath-holding was required in few sequences. 0.1 mmol/kg Gadolinium based contrast (Gadobenate) was injected at the rate of 2.5 ml/sec followed by saline flush and dynamic contrast enhanced MRI (DCE-MRI) with post-contrast fat-suppressed T1W imaging was acquired.

Results and Conclusions: In cirrhosis, there is development of nodules which are initially only microscopically detectable. With progression of cirrhosis, there is development of radiologically detectable regenerative nodules, dysplastic nodules and hepatocellular carcinoma. Amongst these regenerative nodules are completely benign lesions whereas dysplastic nodules, though benign, are considered premalignant; and hepatocellular carcinoma is a malignant condition. Differentiation of benign versus malignant lesions is possible on the basis of enhancement pattern in dynamic contrast enhanced MRI. The signal characteristics of focal lesions and other findings like portal vein thrombosis are helpful, give additional clue to the diagnosis and also helpful in assigning LI-RADS grade to a lesion. Also, MRI characterization after gadolinium based contrast injection was found to be similar to the previous imaging based on non-gadolinium contrast agents.

Introduction
Liver cirrhosis is defined as diffuse process characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodules. Cirrhosis has become the 12th leading cause of death by 2013. Cirrhosis is the main cause of HCC which accounts for 70% to 85% of primary liver cancers and is the 4th most common cancer in males in India. Cirrhosis is characterized by the formation of bridging fibrous and parenchymal nodules, which range from small (<3 mm) in diameter i.e. micronodules, to large (>1 cm) in diameter i.e. macronodules. Well defined dysplastic nodules are generally larger, may be > 2 cm whereas regenerative nodules are usually < 2 cm. There is step-wise progression from regenerative nodules (RN) to hepatocellular carcinoma (HCC) along the pathway of RN, low grade dysplastic nodules (LGDN), high grade dysplastic nodules (HGDN) and finally HCC.

Modalities In Evaluation of Liver cirrhosis

“Cirrhosis” per se is a pathological diagnosis. However clinical, biochemical and radiological examination can be used in evaluation. In patients with cirrhosis, an elevated AFP level is a marker for increased risk of HCC, however serum AFP level measurement has poor accuracy for diagnosis of HCC, and patients with infiltrative HCC may have normal AFP levels. Hence, the use of AFP level does not qualify it as a screening test for HCC. With more advanced HCC, AFP testing is occasionally helpful to confirm a radiologic diagnosis mainly in patients in whom there is some uncertainty about the diagnosis and biopsy is not possible. Patients with later stage disease are more likely to have markedly elevated AFP levels.

Amongst the radiological investigations, MRI is better imaging modality because of high quality

¹Professor and Head, ²Speciality Medical Officer, Lokmanya Tilak Municipal Medical College and General Hospital, Sion, Mumbai, Maharashtra; *Corresponding Author
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Imaging with high intrinsic soft tissue contrast, faster sequences which capture arterial sequences better, lack of ionizing radiation and simultaneous evaluation of background liver parenchyma and the liver lesions. Moreover, gadolinium based liver specific contrast agents are being considered to be the most useful and practical, particularly for lesion characterization. MRI is more sensitive for diagnosis of cirrhotic nodules, with its most important role in cirrhotic patient being the diagnosis and follow up or progression of cirrhotic nodules. Sensitivity of MRI varies with tumor size; however, it has been estimated to be about 100% in HCCs larger than 2 cm.

Nodules and fibrosis- the two main features of cirrhosis, combined in varying proportions result in a wide spectrum morphologic appearances. Liver may be normal in size, may be enlarged early in the disease or shrunken in late disease and shows heterogeneous architecture with surface irregularity, nodularity. Sometimes, there is relative segmental hypertrophy of caudate lobe and left lobe segments II, III; atrophy of the right hepatic lobe and reduction in the transverse diameter (< 3 cm) of the medial segment of left lobe i.e. segment IV.

Regenerative nodules (RN)

Regenerative nodules vary in appearance and can be T1 hypo, iso, or hyper-intense while these are usually T2 hypointense, smaller than 2 cm and show similar pattern of enhancement as the normal hepatic parenchyma. Fat containing nodules can be large (> 1.5 cm). The presence of numerous nodules < 1 cm suggests benignity. T1 hyperintensity may be because of the presence of lipid, protein, or possibly copper. The fibrous septa surrounding RNs appear T1 hypointense and T2 hyperintense.

Dysplastic nodules (DN)

Dysplastic nodules, previously called adenomatous hyperplastic nodules are premalignant, usually T1 hyperintense, while being iso or hypointense on T2W images. Low-grade dysplastic nodules (LGDNs) are not considered premalignant, whereas high-grade dysplastic nodules are premalignant, progress to HCC more frequently, and may even be associated with increased alpha-fetoprotein levels. LGDNs show same enhancement characteristics as that of the background liver parenchyma on all dynamic phases. HGDNs tend to show early homogeneous arterial enhancement post gadolinium contrast enhancement and fade to isointensity but do not show washout.

Hepatocellular carcinoma (HCC):

HCC is reported to develop in dysplastic nodule when “nodule within a nodule” appearance i.e. a focus of T2 hyperintensity within a T2 low signal intensity nodule is noted. Arterial phase hyperenhancement is the most common, sensitive and important imaging finding in the diagnosis of HCC, but can also be seen in HGDNs, AP shunts and in a variety of benign and malignant hepatic lesions. The key distinguishing feature of HCC from other lesions is the development of delayed “washout”; defined as arterially enhancing nodules becoming “hypointense” compared to the background liver on the delayed phase imaging. HCCs greater than 2 cm in size have high diagnostic sensitivity as they tend to show washout. However, HCCs smaller than 2 cm may not show washout. Hypovascular HCCs are uncommon.

HCCs exhibit hypointensity on hepatobiliary phase images, except for well differentiated HCCs which may retain the contrast agent. Delayed pseudocapsule enhancement of hepatic nodules aids in the diagnosis of HCC, and is particularly helpful in lesions that do not show classical features of HCC on dynamic imaging.

HCC may demonstrate slow growth hence only nodules that are stable for 2 years are considered benign. HCCs can be focal (nodular), massive, and diffuse/infiltrative with the nodular type being most common and further classified as solitary or multi-focal. A rare variant of nodular subtype shows rim enhancement on arterial phase imaging, more progressive behavior with rapid interval growth, requiring short-term follow-up and prompt therapy. Diffuse HCCs are usually large, have ill-defined boundaries, almost always associated with portal venous thrombus; which can be bland or most of the time tumoral in nature and usually have very high alpha-fetoprotein levels. A very close differential of diffuse HCCs are the areas of confluent fibrosis which has similar signal intensity and enhancement features as fibrotic septa but unlike neoplasms, it typically has a wedge like or geographic shape with straight or concave borders, radiating from the portal hilum to contact the liver surface, retracts the overlying hepatic capsule, shows progressive contrast enhancement and is associated with progressive volume loss if follow-up studies are performed.

International guidelines regarding radiological diagnosis of HCC

In the setting of liver cirrhosis, international guidelines have set the noninvasive criteria for HCC diagnosis; which relies on post-contrast dynamic imaging techniques with at least three different phases (arterial, portal venous, and equilibrium phases). Functional imaging like DWI and hepatobiliary specific MR contrast agents are useful in the detection and characterization of borderline hypovascular lesions. HCC diagnosis is established by the detection of contrast hyperenhancement in the arterial phase (wash-in) and hypoenhancement in the portal or delayed phase (wash-out) with dynamic MDCT or MRI. This behavior is defined as “HCC radiological hallmark”.

Eastern guidelines state that irrespective of the dimensions of the nodules, HCC diagnosis can be established by the typical enhancement pattern even in lesions smaller than 1 cm. According to the updated American Association for the Study of Liver Diseases (AASLD) guidelines, the detection of the typical enhancement pattern at one single imaging modality in nodules larger than 1 cm suffices for diagnosing HCC. Recent European Society for the Study of the Liver (EASL) guidelines reinforced that although a single imaging modality is considered sufficient for diagnosing HCC in nodules above 2 cm, nodules of size 1–2 cm should be investigated by two imaging modalities. Both EASL and AASLD guidelines suggest biopsy for all atypical nodules larger than 1 cm.

Standardization of reporting

To reduce the interobserver variability and inconsistency in interpretation and reporting of findings at liver imaging, scoring systems have been developed. In 2012, American College of Radiology developed the
Table 1: The pattern of nodules was as following

<table>
<thead>
<tr>
<th>MRI detected liver lesions</th>
<th>No. of cases (n = 20)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regenerative nodules only</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Dysplastic nodules only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HCC only</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Regenerative nodules with dysplastic nodules</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Dysplastic nodules with HCC</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Regenerative nodules with HCC</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Regenerative nodules, dysplastic nodules and HCC</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

Liver Imaging—Reporting and Data System (LI-RADS) for standardizing terminology and criteria for interpreting and reporting findings of CT and MRI examinations of the liver in patients with cirrhosis or increased risk of HCC. The LI-RADS classifies lesions to five categories ranging from definitely benign to definitely HCC on the basis of several criteria, such as mass-like configuration, increase in size, arterial phase hyperenhancement, portal venous phase or later phase hypoenhancement, presence of tumor capsule, and vein involvement. In the latest 2013.1 version, LI-RADS and UNOS OPTN categorizations have been unified. This version applies to multiphase CT and MRI examinations performed with conventional extracellular contrast materials. It currently, does not apply to hepatobiliary specific gadolinium-based agents.

Observations

A total number of 35 consecutive patients with liver cirrhosis diagnosed by clinical / biochemical / imaging criteria (USG / CT) were included in the study.

Maximum number of patients belonged to age group of 41-50 years and the mean age of our study population was 40.70 years. 23 patients (62.86 %) were male and 12 patients (37.14 %) were female. The most common presenting symptom was abdominal pain, followed by abdominal distension. Amongst the study population, 10 patients (28.6 %) had history of alcohol intake, 8 patients (25.72 %) were HBsAg positive while 3 patients (8.6 %) were HCV positive. Of these, 16 patients had got AFP levels done, of which, 7 patients (43.75 %) had normal AFP levels of which 4 had no cirrhotic nodules, 2 had hepatocellular carcinoma of grade LR-5B (1 focal and 1 diffuse) and 1 had hepatocellular carcinoma of grade LR-4A. Of the 9 patients (56.25 %) having raised AFP level, 6 had hepatocellular carcinoma of grade LR-5B (3 focal and 2 diffuse), 1 had diffuse hepatocellular carcinoma of grade LR-4B and 3 had dysplastic nodules of grade LR-3.

Amongst the study population, 27 patients (77.15 %) had focal liver lesions detected in MRI (20 patients i.e. 74.1 % had cirrhotic nodules, whereas 7 (25.9 %) patients had other pathologies) and 8 patients (22.85 %) did not have any MRI detectable lesions. Out of the 20 patients with cirrhotic nodules, the dominant lesion in 12 patients was hepatocellular carcinoma (7 focal and 5 diffusely infiltrating), 5 had regenerative nodules (including 2 which were lipid rich and 1 showing atypical enhancement pattern) whereas 3 had dysplastic nodules. In addition to the dominant lesion, multiple other cirrhotic nodules (regenerative nodules or dysplastic nodules) were noted in 12 patients. 6 patients had Budd-Chiari syndrome (5 of them also having other cirrhotic nodules and 1 without other cirrhotic nodules) while 7 patients did not have any other lesion.

Lesion characteristics: Out of the 12 patients having hepatocellular carcinoma, 7 had focal while 5 had diffusely infiltrating hepatocellular carcinoma. All hepatocellular carcinoma cases were confirmed either histologically, or correlated with imaging on CT or with raised AFP values.

Out of the 7 patients with focal hepatocellular carcinoma, 3 lesions were T1 hypointense, 2 were isointense, and 1 was iso-hyperintense while 1 lesion was a hyperintense with a hypointense component within. 3 lesions were T2 hyperintense, 1 was isointense, 1 was iso-hyperintense and 1 was hypo-isointense while 1 lesion was isointense with a hyperintense component. 2 lesions showed restricted diffusion with corresponding low ADC values while 1 lesion had patchy restriction and 4 lesions did not show restricted diffusion. There was no significant change in signal intensities in dual FFE sequence. In post-contrast sequence, all, except one of the lesions showed typical enhancement pattern i.e. early arterial enhancement with either portal venous or delayed phase washout. 1 lesion showed atypical enhancement pattern with no significant arterial phase enhancement and patchy portal phase enhancement without washout.

Out of the 5 patients with diffuse hepatocellular carcinoma, 2 lesions were T1 hypointense, 2 were hyperintense, and one was isointense. 3 lesions were T2 hyperintense and 2 were hypointense. 3 lesions had restricted diffusion with corresponding low ADC values while 2 lesions had patchy restricted diffusion. None of the lesions showed significant change in signal intensities in dual FFE sequence. In post-contrast sequence, 1 of these lesions showed typical arterial phase enhancement with delayed phase washout, 3 showed arterial phase enhancement without washout while 1 lesion showed peripheral enhancement.

Out of the 3 patients with Dysplastic nodules, 2 lesions were T1 hyperintense and 1 was isointense. 2 lesions were T2 hyperintense and 1 was hypointense. None of the lesions showed restricted diffusion. None of the lesions showed significant change in signal intensities in dual FFE sequence. In post-contrast sequence, 2 of the lesions showed portal venous phase enhancement without washout, whereas 1 lesion showed arterial phase enhancement without washout.

Out of the 5 patients with Regenerative nodules, 2 lesions were T1 hyperintense, 1 was iso-hyperintense and 2 lesions were isointense. 3 lesions were T2 isointense and 2 lesions were hypointense. None of the lesions showed restricted diffusion. 2 of the lesions showed loss of signal in out-of phase scan s/o lipid deposition. In post-contrast sequence, 2 of the lesions were isoenhancing to rest of the liver parenchyma, 2 were non-enhancing while 1 lesion was hypoenhancing.

Portal Vein Thrombosis: 5 patients (14.3 %) had portal vein thrombosis, of which, 3 had definite tumor thrombus, 1 had probable tumor thrombus and 1 had bland thrombus.

LIRADS Grade of various lesions: Out of the study population, 8 patients did not have any MRI detectable lesions hence LIRADS grade was not applied. Out of the 27 patients having MRI detectable liver lesions, the dominant lesion was characterized under LIRADS grading system. 10
lesions (28.57%) were LR-1, of which, 2 were regenerative nodules and 8 (29.6%) were other pathologies. 2 lesions were LR-2 and LR-4A each 3 were LR-3 and LR-4A each while 7 (20%) were LR-5B. LIRADS distribution of the lesions is as follows (Table 2).

USG was done in all patients. USG was able to identify 14 (51.85% of the lesions) amongst the 27 patients in whom lesions were identified on MRI. CT was done in 11 patients, of which 10 patients had focal lesions detected in MRI. CT was able to identify 8 (80%) amongst these 10 lesions while 2 (20%) were not detectable (regenerative nodules and a small cyst). 

**Results and Discussion**

The observations and results were tabulated under various headings and then correlated with various past studies.

With respect to the mean age and gender distribution, our observations were concordant with the previous studies (10, 3).

In our study, maximum i.e. 15 patients (42.9% of the cases) were recently diagnosed cases of liver cirrhosis, followed by 8 patients (22.9% of the cases) who were diagnosed within last 5 years. 6 patients belonged to 6-10 yrs duration group, 3 patients in 11-15 yrs group, 2 patients in 16-20 yrs group and 1 patient in 21-25 yrs group. To the best of our knowledge, there is no significant literature available pertaining to the duration of diagnosed cirrhosis in patients with radiologically diagnosable liver changes. Although the duration of diagnosed cirrhosis observed in our study population was less, this is most likely spurious. The proposed factors contributing to this false result are – The center being a tertiary care hospital, patients referred to this hospital are almost always treated for a significant duration of time outside, majority of them getting only symptomatic treatment without much workup, and thus causing delay in the actual diagnosis. Also, patients coming to our hospital were from lower socio-economic strata hence negligent about health conditions.

No significant correlation was observed with raised or normal AFP values as similar lesions were observed in both the groups. This is in concordance with the other studies (11, 12).

Out of the 27 patients having focal lesions detected in MRI, 20 (74.1%) patients had cirrhotic nodules, whereas 7 (25.9%) patients had other pathologies. Out of the 20 patients with cirrhotic nodules, the dominant lesion in 12 patients was hepatocellular carcinoma (7 focal and 5 diffusely infiltrating), 5 patients had regenerative nodules (including 2 which were lipid rich and 1 showing atypical enhancement pattern) whereas 3 patients had dysplastic nodules. Out of the 20 patients with cirrhotic nodules, in addition to the dominant lesion, multiple other cirrhotic nodules (regenerative nodules or dysplastic nodules) were noted in 12 patients, 6 patients had Budd-Chiari syndrome (5 of them also having other cirrhotic nodules and 1 without other cirrhotic nodules) while 7 patients did not have any other lesion.

**Lesion characterization**

**Hepatocellular carcinoma:** (Figures 2, 3, 4). Findings in our study were correlated with previous studies and were consistent regarding T2 signal intensity. Our study differs in having a considerable number of hepatocellular carcinoma, which were T1 hyperintense. However T1 hypointensity in hepatocellular carcinoma is well known to occur and is usually associated with better tumor grade than T1 hypointense hepatocellular carcinomas (13). The contrast enhancement pattern is similar for focal hepatocellular carcinoma but differs in diffuse hepatocellular carcinoma, many of which showed arterial phase enhancement but no washout (1 patient had arterial phase enhancement with delayed phase washout, 1 patient had peripheral enhancement while 3 patients had arterial phase enhancement but persistent delayed phase enhancement without washout) (3, 14, 15, 16).

**Dysplastic Nodules:** (Figure 5): As compared to previous study done by Quaia et al (3), our study revealed similar (consistent) signal intensities in unenhanced scans and contrast enhancement pattern in 2 patients but different contrast enhancement pattern (arterial enhancement) in 1 patient. However even this patient did not have delayed phase washout hence was consistent with the results of previous studies e.g. done by JA Marrero et al.14

**Regenerative nodules:** (Figure 6) Signal characteristics in our study group are similar on T2 weighted images but differ from this observation on T1 weighted images. However the observations in our study are consistent with the literature stating that regenerative nodules can be iso-hyperintense on T1 weighted images. These differences can be attributed to less number of sample size for regenerative nodules. Enhancement pattern was classical in two of the lesions whereas atypical in the other three. 2 of the lesions were fat containing, one of which showed no enhancement.

**Portal vein thrombosis:** Out of the study population of 35 patients having liver cirrhosis, 4 patients (11.4% of the cases) had portal vein thrombosis and 31 patients (88.6% of the cases) did not have any portal vein thrombosis. All the 4 patients having portal vein thrombosis had diffuse type of hepatocellular carcinoma (amongst total of 5 patients having diffuse hepatocellular carcinoma). Our findings were consistent with the previous results (14, 15).

**LIRADS:** Out of the study population of 35 patients having liver cirrhosis, 27 patients (77.15% of the cases) had MRI detectable liver lesions (cirrhotic nodules as well as other pathologies which are considered) and 8 patients (22.85% of the cases) did not have any MRI detectable lesions. Out of the 27
lesions detected in MRI, 10 (28.57 %) were LR-1, of which 2 were regenerative nodules and 8 (29.6 %) were other pathologies and 7 (20 %) were LR-5B (Hepatocellular carcinomas).

To the best of our knowledge, there is no significant literature available pertaining to exact number or prevalence of different LIRADS lesions in cirrhotic patients.

Our results were consistent with the observations in previous studies regarding detection of lesions in USG or CT (17, 18).

**Conclusion**

The spectrum of liver changes in cirrhotic patients in MRI includes heterogeneity, surface nodularity,
Fig. 4: An ill-defined T1 hypointense, T2 hyperintense lesion in segments VI, VIII showing patchy areas of early arterial enhancement, increasing in portal phase and appearing isointense to rest of the parenchyma in venous and delayed phase without washout. Also seen is hyperintense filling defect showing arterial enhancement in branches of portal vein with non-opacification in portal phase suggestive of tumor thrombus

Fig. 5: Few T1 hyperintense, T2 hypointense lesions showing early arterial enhancement, appearing hyperintense to rest of the liver parenchyma in portal venous and venous phases but isointense in delayed phase i.e. no washout

Cirrhotic nodules are initially only microscopically detectable with progression to development of radiologically detectable nodules later. Regenerative nodules are completely benign lesions, dysplastic nodules though benign, are considered premalignant; and hepatocellular carcinoma, is clearly a malignant condition. Hence, differentiation of

selective lobe atrophy and development of focal lesions like regenerative nodules, dysplastic nodules and hepatocellular carcinoma. Development of portal vein thrombosis, associated findings of portal hypertension like splenomegaly, ascites and collaterals may be found.
benign versus malignant lesions is possible on the basis of enhancement pattern in dynamic contrast enhanced MRI.

MRI best characterizes focal cirrhotic liver lesions. USG can detect focal lesions but cannot reliably characterize them. CT can reliably characterize the focal lesions and differentiate between regenerative nodules and hepatocellular carcinoma, but may not be able to reliably differentiate dysplastic nodules from regenerative nodules or from hepatocellular carcinoma. Hence CT is still less sensitive as well as specific than MRI. MRI is most reliable investigation for suspected hepatocellular malignancy-in detection and also for monitoring of patients in whom the lesions are detected previously. Although ultrasound is used for monitoring the patients in early stages of cirrhosis, MRI has high sensitivity and specificity. The signal characteristics of focal lesions and other findings like portal vein thrombosis are helpful, give additional clue to the diagnosis and also helpful in assigning LIRADS grade to a lesion.

**Abbreviations**


**References**