Chemical shift MRI at 3 T to differentiate hepatocellular carcinoma and non-hepatocellular malignant tumors of the liver

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Authors: K. OZTURK, E. Soylu, G. Savci; Bursa/TR
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Purpose

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy that is the third leading cause of cancer-related deaths worldwide. Beside this, the liver is one of the most common site for metastatic disease accounting for 25% of all metastasis to solid organ [1, 2]. The radiologist has a challenging role in distinguishing these two common entity for determination of prognosis and successful treatment.

MRI is a comprehensive radiological technique that enables detailed information in the evaluation of liver tumors. However, differentiation of HCCs from other malignant liver tumors (non-HCCs), including metastases is not clearly possible with conventional MR techniques and sometimes more advanced techniques or even biopsy maybe necessary [3]. Especially the differentiation may be problematic in patients who have unknown history of extrahepatic malignancy.

In this study, our purpose was to evaluate the diagnostic performance of chemical shift MR imaging in distinguishing HCCs from non-hepatocellular malignant tumors of the liver by means of detecting and estimating intracytoplasmic lipid within the tumors compared to the liver parenchyma.

Methods and materials

In this retrospective study, the patients who have either primary or metastatic malignant liver tumors studied with 3.0-T magnet were evaluated. Thirty-six HCCs and sixty-one non-HCCs (44 women and 53 men; mean age, 58.8 years; age range 30-86 years) were retrieved from the radiology database. Masses smaller than 5 mm were not included to the study to avoid partial volume effect (mean size 35 mm; ranged 6-140 mm). The largest one was evaluated in patients who have multiple masses. Mean region-of-interest values (ROIs) were calculated following three ROIs measurements from solid portion in both tumors and adjacent liver parenchyma.

Lesion types were confirmed by either histopathological examination (on the basis of surgical resection and large core needle biopsy) or follow up studies for at least 12 months (contrast enhanced CT or MR imaging). 57 patients with liver tumors had histopathological proof of the lesion itself, 28 patients with metastatic tumor had histopathological proof for primary tumor itself and tumors were accepted as HCCs in 12 patients who have concurrent liver cirrhosis, elevated tumor markers, rapid enlargement
of the mass during follow up imaging and no any history of extrahepatic primary malignancy (Table 1).

**MR Imaging Technique:** All MR imaging examinations were performed on a 3 T superconducting magnet with the phased array body coil. In all patients chemical shift imaging was performed as a component of MR protocol with 3D FFE gradient-echo breath-hold technique (TR: 3.3 msec, TE: 1.16 and 2.1 msec for out-of-phase and in-phase images, respectively, flip angle of 10 degrees, matrix size: 252x169, FOV: 375x304x200 mm, Voxel size: 1.5x1.8x1.5 mm).

**Analysis:** ROIs measurements of liver masses were made on both in-phase and out-of-phase by keeping operator blinded to the clinical data. A special attention was paid to perform ROI measurement in the center of the tumors to avoid partial volume averaging. Spleen was used as the reference organ that is known to be immune to fatty degeneration.

The percentage of signal intensity (SI) ratios [4] were calculated using the following formulas for all tumors and adjacent normal looking liver parenchyma, respectively;

\[
\text{Ratio} = \left( \frac{\text{tumor SI}_{\text{in-phase}}/\text{spleen SI}_{\text{in-phase}}}{\text{tumor SI}_{\text{opposed-phase}}/\text{spleen SI}_{\text{opposed-phase}}} \right) \times 100 / \left( \frac{\text{tumor SI}_{\text{in-phase}}/\text{spleen SI}_{\text{in-phase}}}{} \right) \times 2.
\]

\[
\text{Ratio} = \left( \frac{\text{liver parenchyma SI}_{\text{in-phase}}/\text{spleen SI}_{\text{in-phase}}}{\text{liver parenchyma SI}_{\text{opposed-phase}}/\text{spleen SI}_{\text{opposed-phase}}} \right) \times 100 / \left( \frac{\text{liver parenchyma SI}_{\text{in-phase}}/\text{spleen SI}_{\text{in-phase}}}{} \right) \times 2.
\]

The subtraction scores were calculated for each lesion by subtracting fat percentage ratios of liver parenchyma from relevant tumors as follow:

\[
\text{Subtraction Score} = (\text{Fat Percentage Ratio of the Tumor}) - (\text{Fat Percentage Ratio of the Liver Parenchyma})
\]

The sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) of the subtraction scores in distinguishing HCCs from non-HCCs were calculated.
<table>
<thead>
<tr>
<th>BIOPSY SITE AND DISTRIBUTION OF TUMORS</th>
<th>n</th>
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<tbody>
<tr>
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<tr>
<td>HCCs</td>
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<tr>
<td>Breast Adenocarcinoma</td>
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<tr>
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<tr>
<td>Stomach Adenocarcinoma</td>
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<td>Cholangiocarcinoma</td>
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<tr>
<td>Squamous Cell Lung Cancer</td>
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<tr>
<td>Small Bowel Carcinoid Tumor</td>
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<tr>
<td>Pancreas Adenocarcinoma</td>
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<td>Small Cell Lung Cancer</td>
<td>n=1</td>
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<tr>
<td>SAMPLED FROM EXTRAHEPATIC ORIGIN</td>
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<td>Squamous Cell Lung Cancer</td>
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<td>Esophagus Adenocarcinoma</td>
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<tr>
<td>Salivary gland tumor</td>
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<td>DIAGNOSIS WITH CLINICAL AND RADIOLOGICAL FOLLOW UP</td>
<td></td>
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<tr>
<td>HCCs</td>
<td>n=12</td>
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<tr>
<td>TOTAL LESIONS</td>
<td>n=97</td>
</tr>
</tbody>
</table>
Table 1: Table shows the list of confirmed histology of the 57 hepatic and 28 extra-hepatic masses; 12 HCCs which is confirmed by follow up.

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Fig. 1: HCCs - Axial GRE T1-weighted scan: Note the signal intensity loss in "out-phase" (b) compared to the "in-phase" image (a). Subtraction score greater than '0' suggests intracelluler lipid in this lesion which is compatible with HCCs.

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Fig. 2: Non-HCCs - Axial GRE T1-weighted scan: Note the signal intensity loss in "out-phase" (b) compared to the "in-phase" image (a). Subtraction score less than '0' suggests that the lesion does not contain intracellular lipid which is compatible with non-HCCs.

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Results

The fat percentage subtraction scores of the hepatic masses measured on in-phase and out-of-phase images ranged between (-) 13.9 to (+) 49.1 for HCCs (Mean; +9.34, SD; 12.25); (-) 44.2 to (+) 20.7 (Mean; -7.73, SD; 12.21) for non-HCCs. The scores were #0 in 33 of 36 for HCCs and <0 in 54 of 61 for non-HCCs (fig. 3). The difference between two groups reached to the statistically significant level by use of the unpaired students t test (p < 0.0001). When a subtraction score of 0 was chosen as a cut-off value the sensitivity, specificity, PPVs, NPVs were found to be 91.6%, 88.5%, 82.5% and 94.7%, respectively.

A crucial part was to include every patients to our study who underwent MRI for malignant liver tumors from January 2012 to October 2015. Only the largest tumors which have enough solid portions for ROI selection was sampled in patients who have multiple masses to prevent any statistical bias, if possible. Three HCCs showed lower subtraction scores yielding false negative result. It is confirmed that two of the lesions had excessive iron deposition which demonstrated by decreased signal intensity on the in-phase images compared with the out-of-phase images (fig. 4), the opposite effect with steatosis [5]. In the remaining case, ROI selection was not proper due to excessive motion artefact (fig. 5).

In seven patients with non-HCCs, subtraction scores showed higher values yielding false positive result. Two of them had iron overload in the liver parenchyma (fig. 6) and in other two cases excessive motion artefact was the main problem to obtain accurate signal intensities. Three out of seven patients (2 pancreas adenocarcinoma and 1 colorectal adenocarcinoma) had no clear explanation for this result.

Images for this section:
Fig. 3: Distribution of fat percentage subtraction scores

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Fig. 4: HCC with iron deposition - Axial T2 weighted FSE image shows the liver lesion indicated by arrow demonstrates uniform signal intensity (a). Axial GRE T1-weighted in-phase (b) and out-of-phase (c) MR images show a decrease in the signal intensity of the lesion on the in-phase image (T2* effect) which is related to deposition of iron.

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Fig. 5: Motion artefacts - ghost lines seen anterior to the abdominal wall due to breathing causes misinterpretation of the subtraction score estimation

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**Fig. 6:** Iron overload in the Liver Parenchyma - Axial T2 weighted FSE image shows that the liver demonstrates decreased signal intensity (a). Axial GRE T1-weighted in-phase (b) and out-of-phase (c) MR images show a decrease in the signal intensity of the liver on the in-phase image (T2* effect) which is compatible with iron overload.

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Conclusion

In stepwise carcinogenesis, HCC involves the following steps: Regenerative nodule, low-grade dysplastic nodule, high-grade dysplastic nodule, small HCC and large HCC [6]. HCCs get originated from the hepatocytes which have ability to produce intracellular lipids [7]. As hepatocytes augment itself in the regenerative nodule-low grade dysplastic nodule phase and continue to produce lipid droplets, it is expected that the amount of intracellular lipid which they possess to will be higher compare to the relevant liver parenchyma. Besides, recent studies show the lipogenetic enzymes are induced in the all developmental steps of HCCs compared with background liver tissue. It is used to say this induction could be associated with fatty changes often seen in well-differentiated hepatocellular carcinomas, known as fatty metamorphosis. Notably, however, no strong correlation was found between the increase in lipogenetic enzyme expression and the differentiation of carcinogenesis [8].

As a consequence of these events, even it is hard to correlate the amount of intracytoplasmic lipid between early and late phases of the HCCs in stepwise carcinogenesis, correlation should be made between the relevant liver parenchyma and HCCs. However metastasis of the liver generally behave as the tumor cells of the primary neoplasm which tend to be lipid avid except some fat-containing primary tumors such as teratoma or metastases from some certain tumors such as liposarcoma, Wilms' tumor and renal cell carcinoma [9]. Almost all non-HCCs have lower intracytoplasmic lipid compare to the relevant liver parenchyma.

In conclusion, chemical shift MR imaging can help to detect minimal intracytoplasmic lipid molecules within HCCs which can help to distinguish HCCs from non-HCCs with high confidence, obviating unnecessary biopsy. Some situations such as iron containing HCCs or any increase of iron level within liver parenchyma as seen in hemochromatosis can change the signal pattern and comparison, also artefacts resulted from excessive motion during the examination seen in patients with poor accommodation can decrease the role of this technique in distinguishing HCCs from non-HCCs.

Personal information

Kerem Ozturk, M.D. Department of Radiology, Medical Faculty, Uludag University, Bursa, Turkey; keremov54@hotmail.com
References


