The value of diffusion weighted imaging for making
differential diagnosis between hepatocellular carcinoma and
dysplastic nodule

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Aims and objectives

Cirrhosis is a result of irreversible chronic liver damage characterized by fibrous septa and a nodular arrangement of the liver. Nodules in cirrhosis can be present as regenerative, sideroblastic or dysplastic and can lead to hepatocellular carcinoma (HCC) (1). Dynamic contrast enhanced magnetic resonance imaging (MRI) is now widely used as a reference test for the noninvasive diagnosis of HCC, and hyperenhancement in the arterial phase and washout in portal venous and/or late phases are characteristic for HCC according to the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines, with no need of biopsy (2-4).

Diffusion-weighted MRI (DW-MRI) has gained attention and can provide qualitative (signal intensity) and quantitative (apparent diffusion coefficient) data about liver masses to differentiate malignant from benign masses (3, 5, 6). DW-MRI can provide information about histological differences related to diseases (7). As the benign cirrhotic liver nodules differentiate and progress to HCC, extracellular space is narrowed and the number of cells is increased. Therefore, movement of water molecules is restricted and the diffusivity of water molecules is decreased (5, 8). There are many studies regarding DW-MRI for differentiating benign and malignant liver masses, but only a small number of them concern the DW-MRI findings of DN and HCC nodules in chronic liver disease. In this study we aimed to propose the contribution of DW-MRI for the differentiation of DN and HCC nodules in cirrhotic liver and to investigate the correlation of ADC values with serum alpha-fetoprotein (AFP) levels and the size of HCC nodules.
Methods and materials

Materials and Methods

Patients

This retrospective study was approved by our Institutional Ethics Committee. The radiology information system (RIS) of our institution was searched for patients for whom MRI reports included the keywords of cirrhosis, chronic liver disease, DN and HCC between August 2012 and September 2013. Patients who received dynamic contrast enhanced abdominal MRI with a DW sequence, age 18 years or older, and having clinical and / or radiological signs of cirrhosis were enrolled in the study. Serum AFP levels of patients enrolled in the study were obtained from the medical records of the hospital information system (HIS).

Magnetic resonance imaging protocol

The dynamic contrast enhanced MRI was performed with a 1.5-T superconducting MR system (Signa HDxt, General Electric Healthcare, Milwaukee, USA) with an 8-channel phased-array body coil. The gradient strength of the system was 50 mT/m and the maximum slew rate was 150 T/m/s. Breath-hold T1-weighted (W) and T2-W SSFSE, fat suppressed T2-W SSFSE, T1-W in-phase and out-of-phase images, 3D FIESTA images and gadolinium-based contrast enhanced dynamic 3D imaging with axial LAVA (for arterial phase at 20-35 sec, for portal venous phase at 60 sec and late images at 180-240 sec) were performed in axial and coronal planes to detect and characterize the lesions for all patients. Before contrast medium administration, DW-MRI was performed using a breath-hold single shot echo-planar spin echo sequence on the axial plane. A total of 20 images were obtained for each patient. The gradient factors used (b values) were 0 and 800 s/mm².

Image analysis

One of the radiologists, who searched the RIS, had collected the clinical data about the patients and images of the lesions investigated. Later, the images of the lesions were evaluated by the two radiologists with experience in abdominal imaging of five and ten years according to the criteria established by AASLD guidelines (2, 3). Both of the two observers were blind to patient identity, clinical findings and serum AFP level. Finally, lesions detected in the liver by dynamic contrast-enhanced abdominal MRI were classified as DN or HCC if they suited the specific criteria set before the image analysis by the consensus of the two observers (Figure 1,2). The maximum diameter (mm) of the HCC and DN was measured using an axial T2-W SSFSE image as a reference. The histopathological diagnoses of the lesions were confirmed by searching the HIS.
The SI of DN and HCC nodules were classified as iso, hypo and hyperintense on DW-MRI at $b = 800 \text{ s/mm}^2$ independently by the two observers and a final decision was reached by their consensus. ADC values of the DN and HCC nodules were obtained from the ADC maps as the largest and possible regions of interest (ROI) measurements fitted to the lesion on the same workstation by one of the two observers. The mean of 3 ROI measurements for lesions greater than 2 cm and 2 ROI measurements for lesions smaller than 2 cm were used to obtain ADC values of the same image. Then the ADC value of normal appearing liver parenchyma (NALP) near to the lesion was measured and the ADC ratio of lesion to NALP was obtained.

**Statistical analysis**

Nodules were grouped as DN or HCC nodules using dynamic contrast-enhanced MRI or histopathological findings. The size, serum AFP levels, SI on DW-MRI, ADC and ADC ratio values of DN and HCC nodules were compared with each other by Student T test and Chi-square test. The Statistical Package for Social Sciences (SPSS version 20.0 Chicago, IL, USA) was used to analyse the data. Numeric data were expressed as mean ± SD or number (percentage), where suitable. The size of HCC nodules was compared with serum AFP levels, ADC and ADC ratio values by Pearson correlation coefficient. Correlation coefficient values between 0.2 and 0.4 were accepted as weak, a value between 0.4 and 0.7 as moderate and a value of > 0.7 as strong correlations. Receiver operating characteristic (ROC) curve analysis was performed to evaluate ADC and ADC ratio values to determine the optimal cut off points for HCC. Statistical significance was set as $p < 0.05$ and was bidirectional.
**Fig. 1:** Figure 1-7. A dysplastic nodule at the 7th segment of the liver. T2-WI (1), fat suppressed pre-contrast T1-WI (2), T1-WI arterial phase (3), T1-WI portal venous phase (4), T1-WI late contrast phase (5), DWI (6) and ADC mapping (7) of the lesion.

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Fig. 2: Figure 1-7. A dysplastic nodule at the 7th segment of the liver. T2-WI (1), fat suppressed pre-contrast T1-WI (2), T1-WI arterial phase (3), T1-WI portal venous phase (4), T1-WI late contrast phase (5), DWI (6) and ADC mapping (7) of the lesion.

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**Fig. 3:** Figure 1-7. A dysplastic nodule at the 7th segment of the liver. T2-WI (1), fat suppressed pre-contrast T1-WI (2), T1-WI arterial phase (3), T1-WI portal venous phase (4), T1-WI late contrast phase (5), DWI (6) and ADC mapping (7) of the lesion.

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Fig. 4: Figure 1-7. A dysplastic nodule at the 7th segment of the liver. T2-WI (1), fat suppressed pre-contrast T1-WI (2), T1-WI arterial phase (3), T1-WI portal venous phase (4), T1-WI late contrast phase (5), DWI (6) and ADC mapping (7) of the lesion.

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Fig. 5: Figure 1-7. A dysplastic nodule at the 7th segment of the liver. T2-WI (1), fat suppressed pre-contrast T1-WI (2), T1-WI arterial phase (3), T1-WI portal venous phase (4), T1-WI late contrast phase (5), DWI (6) and ADC mapping (7) of the lesion.

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**Fig. 6:** Figure 1-7. A dysplastic nodule at the 7th segment of the liver. T2-WI (1), fat suppressed pre-contrast T1-WI (2), T1-WI arterial phase (3), T1-WI portal venous phase (4), T1-WI late contrast phase (5), DWI (6) and ADC mapping (7) of the lesion.

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**Fig. 7:** Figure 1-7. A dysplastic nodule at the 7th segment of the liver. T2-WI (1), fat suppressed pre-contrast T1-WI (2), T1-WI arterial phase (3), T1-WI portal venous phase (4), T1-WI late contrast phase (5), DWI (6) and ADC mapping (7) of the lesion.

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**Fig. 8:** Figure 8-14. MRI findings of a histopathologically confirmed HCC at the 4a segment. T2-WI (8), fat suppressed pre-contrast T1-WI (9), T1-WI arterial phase (10), T1-WI portal venous phase (11), T1-WI late contrast phase (12), DWI (13) and ADC mapping (14) of the lesion.

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Fig. 9: Figure 8-14. MRI findings of a histopathologically confirmed HCC at the 4a segment. T2-WI (8), fat suppressed pre-contrast T1-WI (9), T1-WI arterial phase (10), T1-WI portal venous phase (11), T1-WI late contrast phase (12), DWI (13) and ADC mapping (14) of the lesion.

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Fig. 10: Figure 8-14. MRI findings of a histopathologically confirmed HCC at the 4a segment. T2-WI (8), fat suppressed pre-contrast T1-WI (9), T1-WI arterial phase (10), T1-WI portal venous phase (11), T1-WI late contrast phase (12), DWI (13) and ADC mapping (14) of the lesion.

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**Fig. 11**: Figure 8-14. MRI findings of a histopathologically confirmed HCC at the 4a segment. T2-WI (8), fat suppressed pre-contrast T1-WI (9), T1-WI arterial phase (10), T1-WI portal venous phase (11), T1-WI late contrast phase (12), DWI (13) and ADC mapping (14) of the lesion.

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Fig. 12: Figure 8-14. MRI findings of a histopathologically confirmed HCC at the 4a segment. T2-WI (8), fat suppressed pre-contrast T1-WI (9), T1-WI arterial phase (10), T1-WI portal venous phase (11), T1-WI late contrast phase (12), DWI (13) and ADC mapping (14) of the lesion.

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**Fig. 13:** Figure 8-14. MRI findings of a histopathologically confirmed HCC at the 4a segment. T2-WI (8), fat suppressed pre-contrast T1-WI (9), T1-WI arterial phase (10), T1-WI portal venous phase (11), T1-WI late contrast phase (12), DWI (13) and ADC mapping (14) of the lesion.

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Fig. 14: Figure 8-14. MRI findings of a histopathologically confirmed HCC at the 4a segment. T2-WI (8), fat suppressed pre-contrast T1-WI (9), T1-WI arterial phase (10), T1-WI portal venous phase (11), T1-WI late contrast phase (12), DWI (13) and ADC mapping (14) of the lesion.

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Results

From the RIS, 72 patients met the inclusion criteria and were enrolled in the study. Chronic liver disease was present in all patients. Of the patients, 54 were male (75%) and 18 were female (25%). A total of 82 nodules obtained from the patients were included in the study. Of these, 27 nodules were diagnosed as DN and 55 nodules accepted as HCC on the basis of dynamic multiphasic MRI criteria described by AASLD or histopathological findings. Histopathological evaluation of surgical or tru-cut needle biopsy specimens was confirmed as HCC diagnosis in 15 patients and DN in 10 patients. The mean age of patients who had a diagnosis of DN was 62.22 ± 8.05 (range 51 to 75) years and patients who had a diagnosis of HCC was 64.45 ± 8.04 (range 49 to 79) years (p = 0.241). All lesions detected on dynamic contrast enhanced MRI were visible on DW-MRI and ADC maps.

The mean diameter of DN was 18.49 ± 12.47 mm (range 7 - 68 mm) and of HCC nodules was 72.5 ± 47.96 mm (range 10-201 mm) (p < 0.001). The SI of DN was hypointense in 5 (18.5%) nodules and isointense in 22 (81.5%) nodules, while the SI of HCC nodules was hypointense in 1 (1.8%) nodule, isointense in 5 (9.1%) nodules and hyperintense in 49 (89.1%) nodules on DW-MRI (p < 0.001). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of hyper SI on DW-MRI for diagnosing HCC were 89%, 100%, 100% and 81.8% respectively.

The mean ADC value of DN was 1.25 ± 0.22 and of HCC nodules was 1.03 ± 0.25 (p < 0.001). The mean ADC ratio was 0.96 ± 0.22 in DN and 0.76 ± 0.17 in HCC nodules and was statistically significant (p < 0.001). ROC analysis of the ADC and ADC ratios are summarized in Table 1. A cut off value of 1.10 for ADC and 0.86 for ADC ratio had the best sensitivity, specificity, PPV and NPV for the differentiation of HCC nodules from DN (Table 2). There were negative and insignificant correlations between the size of HCC nodules and ADC and ADC ratio (r = -0.210, p = 0.124 and r = -0.104, p = 0.451 respectively).

Table 1. ROC analysis of ADC and ADC ratio values for detecting HCC nodules.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Area under curve</th>
<th>Std. Error</th>
<th>p</th>
<th>Asymptotic 95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>ADC</td>
<td>0.776</td>
<td>0.054</td>
<td>&lt; 0.001</td>
<td>0.671</td>
</tr>
<tr>
<td>ADC ratio</td>
<td>0.867</td>
<td>0.040</td>
<td>&lt; 0.001</td>
<td>0.789</td>
</tr>
</tbody>
</table>
**Table 2.** Statistical data derived from ADC and ADC ratios to determine HCC nodules in patients with chronic liver disease by DW-MRI.

<table>
<thead>
<tr>
<th>Values</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPD*</th>
<th>NPD**</th>
<th>Accuracy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC #1.10</td>
<td>85</td>
<td>70</td>
<td>73.91</td>
<td>82.35</td>
<td>77.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ADCratio#0.86</td>
<td>80</td>
<td>79.59</td>
<td>78.43</td>
<td>79</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: * PPD; positive predictive value, ** NPD; negative predictive value.

Serum AFP levels were obtained in 50 HCC nodules and in 27 DN. The mean AFP level was 53.02 ± 209.47 µg/L in DN and was 1257.02 ± 4386 µg/L (p < 0.058). There were negative and insignificant correlations between the serum level of AFP and ADC and ADC ratio in HCC nodules (r = -0.175, p = 0.223 and r = -0.042, p = 0.77, respectively).
Conclusion

Dynamic contrast-enhanced MRI is now widely used as a reference test and has a role in the management of HCC according to the previously mentioned AASLD and EASL practice guidelines (2-4). DW-MRI is a newly described imaging method and has a potential use in oncologic imaging. In our study, in addition to other studies, we evaluated the use of DW-MRI in the differential diagnosis between DN and HCC nodules in patients with chronic liver disease and showed that high signal intensity on DW-MRI images, low ADC and ADC ratios, regardless of serum AFP level and tumor size, were related to HCC and could be used for discrimination.

Early detection of HCCs and their differentiation from DN in patients with chronic liver disease is crucial for curative treatment procedures (2, 4). Differentiating nodules in patients with chronic liver disease by imaging methods has gained importance and dynamic contrast enhanced imaging by computed tomography, MRI and ultrasonography (US) are evaluated and hyperenhancement on arterial phase and washout of portal venous or late phases are now used for HCC diagnosis without histopathological confirmation. Among these, MRI is the generally preferred imaging method because of the use of radiofrequency waves, low risk of allergic reactions and giving more data by multiplanar imaging. But the long time for image acquisition, which can be problem for elderly or claustrophobic patients, sensitivity to motion of the patient, intestinal peristaltism or cardiac activity that can produce artifacts on images, and also the high cost of MRI-contrast material and adverse effects of contrast agents such as nephrogenic systemic fibrosis can limit the utilization of contrast enhanced MRI in liver masses (9).

Recently DW-MRI, a fast and unenhanced MRI sequence, was evaluated and it could be shown that HCC nodules were easily detectable and visible by suppressing the signals from the liver parenchyma and vascular structures, and could be used for differentiation from other benign liver masses (3, 10). DN, which is assumed to be a precursor lesion for HCC in patients with chronic liver disease, were hypo or isointense on DW-MRI in our study. Xu et al found that most of the DN were hypo or isointense while most of the HCCs were hyperintense on DW-MRI, similar to our results (7). The difference between histological maturation grade and the amount of cells in DNs and HCCs alter the SI on DW-MRI. Contrast to the surrounding liver parenchyma and microstructure of the HCCs is different because of the increased density of cells, thickened cellular walls and arterial vascular supply. Thus, movement of water molecules is progressively restricted and results in a high SI on DW-MRI while normal appearing liver parenchyma is hypointense (7, 8, 11). The sensitivity of hyperintensity on DW-MRI varied between 67.5% and 95.2% according to recent studies and it was shown that HCCs were generally hyperintense relative to the surrounding liver parenchyma on DW-MRI (3, 7, 8, 10). In agreement with previously published reports we obtained a value of 89%. Although they were significant, the wide range of sensitivity values might be due to different b factors and sequences of DW-MRIIs. Tumor type, maturation grade and necrosis could alter the diffusivity of
water molecules and this should be kept in mind with oncologic imaging by DW-MRI (12). Although we did not evaluate and compare the SI properties of different histopathological grades of HCC on DW-MRI, the histopathological grade of HCCs might affect the SI on DWI and may explain the wide range of sensitivity values.

The SI on DWI is affected by the T2 shine-through effect while the ADC value is not, therefore the exact value of restriction in diffusion can be assessed by the ADC measurements of the lesions, which could be used for differentiating nodules in chronic liver disease (7,11). ADC and ADC ratio values of the HCC nodules were significantly lower than the DN in our study but lower than previously published reports (3, 7). ADC is a measure of signal loss related to the value of a b factor, thus this discrepancy may be related to the high value of b factor we used compared to other studies (13). We found an ADC value of $\leq 1.10$ and an ADC ratio of $\leq 0.86$ as the best cut off points to differentiate HCCs from DN with high sensitivity, specificity, PPV, NPV values.

Serum AFP level is a screening test for HCC with ultrasonography (US), with sensitivity values between 41-65% (14). In our study, we found a negative and insignificant correlation between HCC size and serum AFP levels and HCC ADC and ADC ratios. Using serum AFP level for screening HCC has some limitations because of false positive and negative situations. During pregnancy and for embryonic tumors, AFP can be positive. Also some HCCs are AFP negative (15) and could explain the insignificant correlation.

This study had some limitations. Firstly, inter and intra observer agreement for SI on DW-MRI and measurement of ADC and ADC ratio were not investigated, which could show that our results were reproducible. Secondly, the histopathological confirmation of diagnosis of HCC and dysplastic liver nodules was made for some of the cases. But AASLD and EASL practice guidelines for MRI criteria as a reference test for HCC screening and histopathological confirmation can be challenging in clinical practice, even at a reference hospital. We could also make more homogeneous groups of HCCs, as small or large, and grading of HCCs, to interpret the effect of necrosis and maturation of tumors on ADC values.

In conclusion, our results showed that DW-MRI can be used for differentiating HCC and DN in chronic liver disease on the basis of SI pattern and ADC values. Due to the lack of contrast medium administration and faster imaging, DW-MRI should be added to dynamic contrast enhanced MRI in patients with chronic liver disease.
References


