Focal Liver Lesion Characterisation with Diffusion-weighted MR Imaging: Analysis of Apparent Diffusion Coefficients in Malignant and Benign Lesions

Poster No.: R-0189
Congress: RANZCR-AOCR 2012
Type: Scientific Exhibit
Authors: S. Davis, J. Chang, A. Moghaddam, N. Saad; AU
Keywords: Liver, MR-Diffusion/Perfusion, MR, Diagnostic procedure, Cancer, Neoplasia, Metastases
DOI: 10.1594/ranzcraocr2012/R-0189

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Purpose

To retrospectively compare the magnetic resonance imaging (MRI) apparent diffusion coefficient (ADC) values for focal liver lesions (FLL) and establish if the ADC ratio of the FLL to liver parenchyma can accurately distinguish benign from malignant lesions and to determine if ratio values can improve sensitivity and specificity in determining malignancy when compared to absolute ADC values [1-3].

Diffusion weighted (DW) imaging has been validated in both the detection and characterization of focal liver lesions. Recent studies demonstrate that with the use of low b-values (below 100 sec/mm2), DW imaging provides greater sensitivity in the detection of lesions relative to T2-weighted imaging [1, 4-6]. When integrated with higher b-values (> 500 sec/mm2), quantitative assessment may be made using ADC maps [1]. Malignant lesions typically demonstrate impeded diffusion relative to liver parenchyma and have equal or lower ADC values compared to normal liver [3]. Investigators have attempted to set quantitative ADC threshold values for lesion characterization and in 2010, a meta-analysis by Xia et al compared 14 of these studies and reported a sensitivity ranging from 0.74-1.0 (mean, 0.91) and specificity of 0.77-1.00 (mean, 0.93) [7].

Limitations of using absolute threshold values are related to lack of standardization, including differences between breath-hold and respiratory-triggered acquisitions and the choice of b values [3,8]. Agnello et al calculated ratio ADC values for benign liver lesions, including focal nodular hyperplasia and hepatocellular adenoma, taking into account the ADC values of the lesion and surrounding liver [2]. We plan to expand on this research and analyze the ADC ratio values on high-b-value DW imaging of both malignant and benign lesions and establish if sensitivity and specificity in determining malignancy can be improved when compared to absolute ADC values [1-3].
Methods and Materials

This single center, retrospective study included consecutive patients identified in the radiology database who underwent MR imaging of the liver between November 2007 and February 2010 and who had at least one confirmed focal liver lesion. DW sequences were performed as part of our routine liver imaging protocol.

A total of 117 patients were identified. Forty-six patients were excluded for the following reasons: no DW images on the picture archiving and communication system (n = 4), focal liver lesions measuring less than 1 cm in diameter (n = 10), treated HCC or metastasis (n = 12), no reference standard available (n = 20). In the presence of multiple hepatocellular lesions, a maximum of four lesions (largest) were recorded per patient.

On the basis of these criteria, the final study population included 71 patients (mean age, 52 years; range, 21-80 years) with 87 hepatic lesions, and of these, 31 were men and 40 were women.

Reference Standard

The reference standard for the diagnosis of benign and malignant lesions were findings on histopathologic analysis of biopsy, or typical patterns on MR images, with follow-up for at least 1 year. Studies were reviewed by NS, a radiologist with 8 years experience in abdominal MRI. Diagnosis of lesion type was based on histopathologic findings in 25 lesions (21 malignant, 4 benign) and on imaging findings in 62 lesions (10 malignant, 52 benign).

Imaging findings were based on established criteria. HCC was considered hyperintense on T2-weighted images and of variable intensity on T1-weighted images. Lesions demonstrate intense enhancement during the arterial phase of dynamic gadolinium-enhanced imaging, are isointense during the portal venous phase and show washout of contrast material relative to the surrounding liver during the delayed phase [9].

Metastases appear hypo to isointense on T1-weighted sequences and iso to hyperintense on T2-weighted sequences. Hypervascular metastases show marked gadolinium contrast enhancement and hypovascular metastases are seen as hypointense masses that may have an enhanced peripheral rim [10].

FNH is iso to hypointense on T1-weighted images and iso to hyperintense on T2-weighted images [11,12]. A central scar may be demonstrated which is hyperintense on T2-
weighted images [13]. FNH shows very intense homogeneous enhancement during the arterial phase of a dynamic contrast-enhanced sequence [12,14].

Adenomas are mildly hypointense to moderately hyperintense on T1-weighted images and mildly hyperintense on T2-weighted images [12]. They show a blush of homogeneous enhancement in the arterial phase and approach isointensity in later phases of dynamic gadolinium-enhanced imaging [12].

MRI and DWI Technique

Patients were examined with a 1.5-T Siemens Avanto MR system, using body array surface coils. The protocol included a coronal breath-hold T2 HASTE sequence, an axial T2-weighted turbo spin-echo sequence and axial in and out of phase T1 weighted sequence. An axial breath-hold three-dimensional T1-weighted VIBE (fat-suppressed volume interpolated gradient echo) sequence was performed before and after dynamic IV injection of 10ml of Disodium Gadoxetate (Primovist) or 0.1 mmol per kilogram of body weight of nonspecific gadolinium chelate, followed by a 10mL saline administered by hand injection. Hepatic arterial-dominant and portal venous phases were performed at 20-25 seconds and 60-70 seconds after contrast material injection respectively, followed by equilibrium phase sequences at 180-200 seconds, 10 minutes and 20 minutes after contrast material injection.

DW images were acquired with an axial echo-planar diffusion weighted sequence (TE 72, TR 1700) using respiratory triggered technique with b values of 50, 400 and 800 sec/mm2.

Analysis of DW Images

Pixel-based ADC maps were obtained with a commercial workstation utilising a monoexponential fit. The largest possible region of interest (ROI) was calculated for each lesion using a closed polygon, which was initially obtained on the DW images then copied to the ADC maps for standardization. If the lesion was not visualized on DWI, then ROI was determined using T2-weighted and/or contrast enhanced T1-weighted images. Three ROIs of at least 1cm were placed in the adjacent liver parenchyma, in the same lobe as the lesion and if possible also in the adjacent lobe. ROI placement was carefully and consistently performed to avoid main branch blood vessels, liver periphery, gallbladder and motion artifacts.

ADC ratio was calculated for each lesion using the formula $\text{ADC}_{\text{Le}} / \text{ADCLi}$, where $\text{ADC}_{\text{Le}}$ is the ADC of the lesion and $\text{ADCLi}$ is the average value of the 3 parenchymal values.
Results

Eighty-seven FLLs (29 malignant, 58 benign) were included. Lesions ranged in size from 10mm to 100mm with an average size of 29mm. 27 lesions were located in the left lobe of the liver and 60 in the right lobe. Among the included lesions, there were 21 HCCs, 9 metastasis, 31 FNHs, 4 adenomas, 18 haemangiomas and 4 cysts. (Table 1) (Images 1 - 8 demonstrate example cases.)

The mean ADC ratio value for malignant lesions was 1.02 and for benign lesions was 1.40. Note the mean ADC value for benign lesions was significantly higher than that of malignant lesions with a p-value of <0.0001. (Table 2 & 3).

With a cut off ratio value of 1.0, the ADC ratio had a sensitivity of 78% and a specificity of 83% for differentiating benign from malignant lesions with an area under the curve value of 0.77.
Table 1: Included lesions by type, number and ADC value

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number of lesions</th>
<th>Mean ADC</th>
<th>Mean ADC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyst</td>
<td>4</td>
<td>2.08</td>
<td>1.88</td>
</tr>
<tr>
<td>Haemangioma</td>
<td>18</td>
<td>1.70</td>
<td>1.70</td>
</tr>
<tr>
<td>FNH</td>
<td>31</td>
<td>1.25</td>
<td>1.20</td>
</tr>
<tr>
<td>Adenoma</td>
<td>4</td>
<td>1.11</td>
<td>1.03</td>
</tr>
<tr>
<td>HCC</td>
<td>21</td>
<td>1.18</td>
<td>1.09</td>
</tr>
<tr>
<td>Metastasis</td>
<td>9</td>
<td>0.94</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Table 2: Statistical comparison of benign and malignant lesions by mean ADC ratio value

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number</th>
<th>ADC Ratio Mean (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>29</td>
<td>1.02 (0.94,1.10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Benign</td>
<td>58</td>
<td>1.40 (1.30,1.50)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Graph: ADC Ratio Values for Benign and Malignant Focal Liver Lesions.

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**Fig. 1:** Metatasis (Colorectal - Biopsy proven). T2, T1 - Arterial (narrow window), T1 - 20 Min delayed, DWI b50, ADC, ADC with ROI values (Top left to bottom right). Segment VII lesion is mildly hyperintense on T2 and demonstrates subtle arterial phase enhancement with washout at 20 minutes. Lesion is hyperintense on DWI and is hypointense on ADC with ratio value of 0.84.

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**Fig. 2:** Adenoma (Biopsy proven). T2, T1 - Arterial, T1 - 20 Min delayed, DWI b50, ADC, ADC with ROI values (Top left to bottom right). Segment V lesion is iso-hypointense on
T2 and demonstrates arterial enhancement with central washout at 20 minutes. Lesion is mildly hyperintense on DWI and ADC with ratio value of 1.06. Steatotic liver.

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**Fig. 3:** HCC (Biopsy proven). T2, T1 - Arterial, T1 - 20 Min delayed, DWI b50, ADC, ADC with ROI values. Segment II lesion is hyperintense on T2 and demonstrates capsular arterial enhancement with washout at 10 minutes. Lesion is hyperintense on DWI and is hypointense on ADC with ratio value of 0.89.

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**Fig. 4:** Haemangioma (Biopsy proven). T2, T1 - Arterial, T1 - Portal Venous, DWI b50, ADC, ADC with ROI values (Top left to bottom right). Small Segment VII lesion is hyperintense on T2 and demonstrates intense diffuse arterial enhancement. Lesion is hyperintense on DWI and is hyperintense on ADC with ratio value of 1.9. Steatotic liver.

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**Fig. 5:** Metatasis (Melanoma - Biopsy proven). T2, T1 - Arterial, T1 - 20 Min delayed, DWI b50, ADC, ADC with ROI values (Top left to bottom right). Segment VII lesion is hyperintense on T2, demonstrates peripheral arterial enhancement and is hypointense at 20 minutes. Lesion is hyperintense on DWI and is hypointense on ADC with ratio value of 0.87. Steatotic liver.

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**Fig. 6:** Adenoma (Biopsy proven). T2, T1 - Arterial, T1 - 10 Min delayed, DWI b50, ADC, ADC with ROI values (Top left to bottom right). Segment VI lesion is iso-intense on T2 and demonstrates enhancement on all phases to 10 minutes. Lesion is hyperintense on DWI and is hyperintense on ADC with ratio value of 1.14. Steatotic liver.

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**Fig. 7:** FNH (Biopsy proven). T2, T1 - Arterial, T1 - 10 Min delayed, DWI b50, ADC, ADC with ROI values (Top left to bottom right). Segment IV lesion is iso-hypointense on T2 and demonstrates enhancement on all phases to 10 minutes. Lesion is hyperintense on DWI and is hyperintense on ADC with ratio value of 1.7.
**Fig. 8:** HCC (Biopsy proven). T2, T1 - Arterial, T1 - 20 Min delayed, DWI b50, ADC, ADC with ROI values (Top left to bottom right). Segment II/III lesion is hyperintense on T2 and demonstrates patchy arterial enhancement with washout at 10 minutes. Lesion is hyperintense on DWI and is hypointense on ADC with ratio value of 0.95.
Conclusion

Our study demonstrates that benign liver lesions have less restricted diffusion than surrounding liver parenchyma and that with the use of quantitative assessment, the ratio of ADC values for liver lesion relative to liver parenchyma, benign lesions can be differentiated from malignant lesions with a sensitivity of 78% and specificity of 83%.

Our results are consistent with results from previous studies. The mean ADC values summarized in Table 4 compare the mean ADC values from our study with the ADC values of 211 FLLs calculated by Parikh et al [1]. Excluding metastases, Parikh's results are consistently between 11% to 34% greater than the ADC values of our calculated lesions. We hypothesize that the difference in these results may be due to the differing choice of b-values (Parikh’s 0, 50, 500 sec/mm² compared to 50, 400, 800 sec/mm² in our study) [1]. Higher variation in ADC values for metastasis is unclear, however, maybe related to the variable cellular composition of these lesions [15].

Agnello et al compared ADC ratio values for FNH and adenomas, in an attempt to standardize differences between varying b-values used in DWI sequences [2]. Our data demonstrates that when ADC ratio values are used to differentiate benign lesions from malignant lesions, a sensitivity of 78% and specificity of 83% is achieved by using a cutoff value of 1.0.

Investigators in a recent meta-analysis of studies using absolute ADC threshold values to determine malignant or benign FLLs, report a sensitivity ranging from 0.74-1.0 (mean, 0.91) and specificity of 0.77-1.00 (mean, 0.93) [7]. Accuracy was found to decrease in studies that include benign hepatocellular lesions such as FNH and hepatocellular adenomas and our results are consistent with these findings [3].

In conclusion, our results are consistent with published data for quantitatively distinguishing benign from malignant hepatic lesions. These studies have used an absolute ADC threshold for differentiating lesions and limitations have included variances in selected b-values as well as utilisation of breath-hold or respiratory-triggered acquisitions. We believed that by calculating ADC ratio values for liver lesion relative to liver parenchyma, results are standardized regardless of technical factor variations, while still providing diagnostic accuracy.
Table 4: Mean ADC values by lesion type compared with values from study by Parikh et al [1]

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References


