

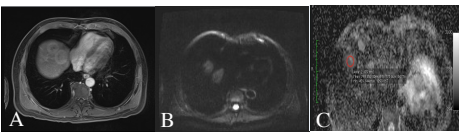
# The Clinical Use of Diffusion-Weighted Magnetic Resonance Imaging for Oncological Biomarkers

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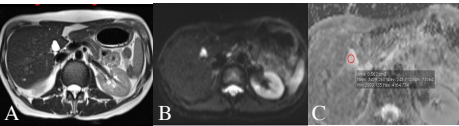
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**Target Audience:** This study will benefit clinicians, including radiologists and interventional radiologists, and institutions that have not incorporated diffusion-weighted MRI as part of their general oncologic imaging practice.

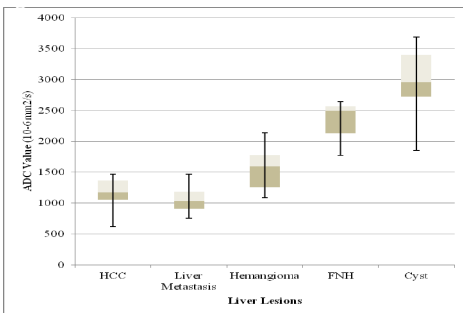
**Purpose:** Diffusion-weighted magnetic resonance imaging (DW-MRI) has been suggested as a promising, non-invasive, and quantitative tool to detect lesions because the acquisition neither requires the use of exogenous contrast agents that may cause nausea in patients nor involves ionizing radiation. However, according to the 2009 consensus paper on DWI [1], global implementation of DW-MRI as a means of assessing cancer face challenges due to lack of qualitative and quantitative assessments and no accepted standards for measurements and analysis. The purpose of this study was to address this issue by assessing a recently implemented liver DWI protocol at our institution - City of Hope National Medical Center - for characterizing malignancy of liver lesions, and thereby emphasize the practice of quality assessments to institutions utilizing DWI protocols and promote widespread standardization.



**Figure 1:** Example of ADC map measurements for malignant liver lesion (HCC). A. T1-weighted image post-contrast. B. Diffusion-weighted image. C. ADC map using b=50 and b=500 s/mm<sup>2</sup>.



**Figure 2:** Example of ADC map measurements for benign liver lesion (cyst). A. Axial T2-weighted image. B. Diffusion-weighted image. C. ADC map using b=50 and b=500 s/mm<sup>2</sup>.



**Figure 3:** Summary of Liver lesions. Mean ADC value of malignancies (n=25) was  $1.081 \times 10^{-3} \text{ mm}^2/\text{s}$ , while mean ADC value of benign lesions (n=22) resulted in  $2.13 \times 10^{-3} \text{ mm}^2/\text{s}$ .

**Methods:** The Institutional Review Board approved this retrospective study to review MRI Abdomen exams from October 2011, of which marked the start of date of DWI sequences, to April 2012 and waived the requirement for informed consents. The study included 55 patients with liver lesions and whom had completed a conventional MRI Abdomen (T2-weighted axial, T2-weighted fat-saturated free breathing, axial T1-weighted, coronal T2-weighted, and coronal T1-weighted sequences) and axial free-breathing DW-MRI with variable b-factors of 0, 50, 100, 500, and 800 sec/mm<sup>2</sup> [TR/TE, 5300/85; acquisition matrix: 192 x 82; slice thickness: 6mm; flip angle: 90°; bandwidth: 1736; FOV: 189 x 355; 150 slices]. All MR images were acquired on a 3.0 T MR System (Avanto, Siemens Medical systems, Erlangen, Germany). ADC maps were calculated on a pixel-by-pixel basis with Osirix software (v. 3.9), using two b-values: 50 and 500 sec/mm<sup>2</sup>. A region of interest of suspected liver lesion was manually drawn on each ADC map, while using the T1- and T2-weighted images as references. A confirmed malignant lesion shown on a T1 weighted image, DW image, and ADC map can be seen in **Figures 1a, b, and c**, respectively; a confirmed benign lesion drawn in a similar process can be viewed in **Figures 2a, b, and c**. The minimum, 25<sup>th</sup> percentile, median, mean, 75<sup>th</sup> percentile, and maximum of the ADC values were calculated using Microsoft Excel software. Student's t-test was performed to determine significance between ADC mean values of malignant and benign liver lesions.

**Results:** Excluding eight lesions either due to inconsistent scanning parameters or too miniscule to be detected on DWI, a total of 47 lesions were examined. Based on the confirmation from one experienced radiologist (J.P.) and pathology reports, 25 lesions were malignant and 22 lesions were benign. Malignant lesions included metastases and hepatocellular carcinoma (HCC), while benign lesions comprised of cysts, hemangiomas, and focal nodular hyperplasia (FNH). Area sizes of regions of interest ranged from 0.22cm<sup>2</sup> to 24.3 cm<sup>2</sup>. Mean ADC value of malignancies (n=25) was  $1.081 \times 10^{-3} \text{ mm}^2/\text{s}$ , while mean ADC value of benign lesions (n=22) resulted in  $2.13 \times 10^{-3} \text{ mm}^2/\text{s}$ . **Figure 3** summarizes the range of ADC values for the 47 lesions of which were categorized either as a HCC, hepatic metastasis, hemangioma, FNH, or cyst. The Student's t-test showed that mean ADC value of malignant lesions was significantly less than that of benign lesions ( $p < 0.0001$ ). Within the benign group, FNH were statistically different from cysts ( $p = 0.0079$ ), and hemangiomas were significantly different from cysts ( $p < .0001$ ). However, no statistical differences were found between FNH and hemangiomas ( $p = 0.24$ ), and none between HCC and metastases ( $p = 0.14$ ).

**Discussion:** These findings validated a previous study that reported ADC values for HCCs, metastases, and hemangiomas to never surpass  $2.5 \times 10^{-3} \text{ mm}^2/\text{s}$  [2]. Our study results confirm the promising use of City of Hope's DWI protocol in distinguishing benign lesions from those of malignant, and foresee ADC values in evolving as essential oncological biomarkers and tools for drug development. Some limitations to our study was small sample size (n= 47) due to the recent implementation of the DWI protocol at our institution, and poor DWI quality in some cases, possibly caused by patient motion (respiratory or peristaltic). The variability in tumor sizes may have caused a wide range in ADC values.

**Conclusion:** This study has demonstrated the ability to successfully differentiate benign from malignant liver lesions using a DW-MRI protocol currently implemented at City of Hope National Medical Center. Our findings are consistent with previously published reports and further validate the utility of DW-MRI for diagnostic liver imaging. This study not only emphasizes the practice of qualitative and quantitative assessments of institutional DWI protocols but also the benefit of adopting DWI as a standard sequence in a liver MRI protocol. This preliminary study has opened many future research avenues, such as investigating the utility of DW-MRI as early biomarkers for treatment outcomes of therapies that induce cell apoptosis. We also plan to correlate ADC values with biological markers as initially explored by Heijmen et al. [3] who had shown a correlation between ADC values and BCL-2 expression for colorectal cancer patients. These results from future studies may suggest diffusion-weighted imaging and ADC maps as advantageous methods to safely test the efficacy of various treatments and also determine the ideal treatment for individual patients based on biological factors of interest.

**References:** [1] Padhani A, Liu G, Koh D, et al. Neoplasia. 2009; 11(2): 102-25. [2] Goshima S, Kanematsu M, Kondo H, et al. J of Mag Res Imaging. 2008; 28: 691-697. [3] Heijmen L et al. Eur Radiol 2012; doi 10.1007/s00330-012-2654-4.