# Quantification of Liver Tumor Necrotic Fraction Using Diffusion-Weighted PROPELLER MRI

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## Introduction

Diffusion-weighted imaging (DWI) permits noninvasive interrogation of tissue water mobility. DWI has increasingly been applied in oncologic applications for tumor detection [1], characterization of lesion types [2] and tissue heterogeneity [3], and evaluation of microstructural changes after therapy [4]. Recent studies have demonstrated a strong correlation between tumor apparent diffusion coefficient (ADC) and tumor necrotic fraction (NF, ratio of necrotic to overall tumor volume) [5]. Intra-tumoral heterogeneity has been studied as an effective biomarker for evaluation of therapy response [3]. The purpose of our study was to assess the use of DWI techniques for *in vivo* quantitative liver tumor NF measurements in the VX2 rabbit model. We tested the hypothesis that multi-shot DW-PROPELLER [6] improves the accuracy of liver tumor NF measurement compared to single-shot DW-EPI.

## Method

***MRI*** All imaging experiments were performed on Sonata 1.5T clinical MR scanner (Siemens Medical Solutions). VX2 liver tumor rabbits were imaged using a single-channel head coil. Axial anatomic images with 3 mm thickness covering the entire tumor volume were acquired using a T2-weighted TSE sequence. DWI scans using both single shot DW-EPI and multi-shot DW-PROPELLER were performed at identical axial slice positions using the following imaging parameters. Single shot DW-EPI: TR/TE=3600/86ms, 1.5kHz/pixel BW, 5/8 partial Fourier, EPI factor = 88, 6 signal averages. Multi-shot DW- PROPELLER: TR/TE = 3600/68ms, 400 Hz/pixel BW, ETL = 17, 4 signal averages. The common imaging parameters for both sequences: 200 $mm^2$ FOV, 128 matrix (1.6 x 1.6 $mm^2$), non-selective fat saturation and acquisition during free-breathing with respiratory bellows triggering. We applied diffusion weightings of b = 0, 500 and 1000 s/$mm^2$ along the readout direction. In several tumors, an additional series of high-resolution DW-PROPELLER images were acquired using a 256 matrix (0.8 x0.8 $mm^2$) for comparison purposes.

***Image Analysis*** Data analysis was performed offline using Matlab software. For each tumor slice, an ADC map was generated on a pixel-by-pixel basis from each series of DWIs. Tumor ROIs at each slice were drawn on the b=500 s/ $mm^2$ DWI and applied to the corresponding ADC map. ADC values of all voxels of the entire tumor volume were classified into two tissue populations by using the K-means clustering algorithm [3]. High and low ADC populations representing necrotic and viable tumor tissues were differentiated within our classification maps as bright and dark voxels, respectively. Whole tumor NF was calculated by dividing the number of bright (necrotic) voxels by the total number of voxels included within the tumor ROIs.

***Histological Analysis*** Each rabbit was euthanized after imaging. Tumors were sliced at 3 mm intervals in the axial plane to correspond to the plane of the MR images. A 4 μm section of each slice was stained using hematoxylin and eosin (H&E) to identify tumor necrosis. Histological slides were digitized with x40 optical magnification using a multispectral imaging system (Nuance, CRI, Inc., Woburn, MA). Magnified portions were stitched together for inspection of the whole tumor area (PanaVue ImageAssembler, QC, Canada). H&E cell staining and cell morphology were characterized by an attending pathologist to assess tumor borders and areas of tumor tissue necrosis. Necrosis and whole tumor areas were measured using ImageJ software.

***Statistical Analysis*** DWI NF measurements were compared to corresponding gold-standard histological NF measurements using a Pearson's correlation test with α=0.05.

## Results

We compared DWI to histological NF measurements in a total of 10 liver tumors in 5 VX2 rabbits. DW-PROPELLER NF was highly correlated with histological NF ($r = 0.89$, $p < 0.001$), while DW-EPI NF was not well correlated ($r = 0.16$, $p = 0.65$) (**Fig.1**). Qualitatively DW-PROPELLER provided superior image sharpness and less distortion than DW-EPI (**Fig.2**). Necrotic and viable tumor tissues were well differentiated based on K-means clustering analysis of the ADC maps. These DWI-based tissue classification maps corresponded well with the H&E slides (**Fig.2**). A representative set of high-resolution DW-PROPELLER images demonstrated the potential for improved spatial characterization of intra-tumoral heterogeneity (**Fig.3**).

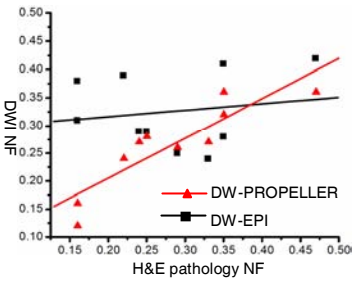
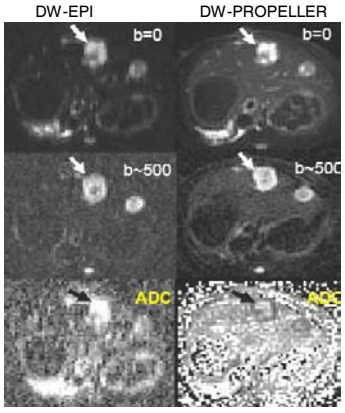



**Fig. 1** NF measurement **c**omparison in each tumor between DW-EPI/DW-PROPELLER and H&E pathology analysis.



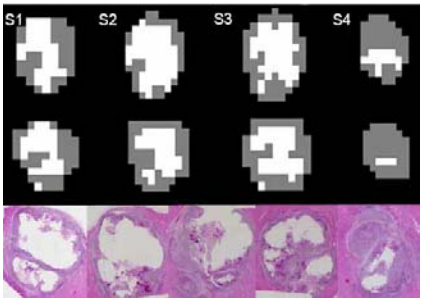




**Fig 2.** Left panel: DWIs and corresponding ADC maps of a liver tumor (arrows) acquired using DW-EPI and DW-PROPELLER. Right panel: Classification of necrotic and viable tumor tissues based on ADC (1st row: DW-EPI, 2nd row: DW-PROPELLER) on each slice (S1-S4) through the tumor and corresponding H&E slides. White/grey areas represent necrotic/viable tumor tissues, respectively. On H&E slides, liquefied necrotic areas were surrounded by purple areas representing viable tumor tissues.

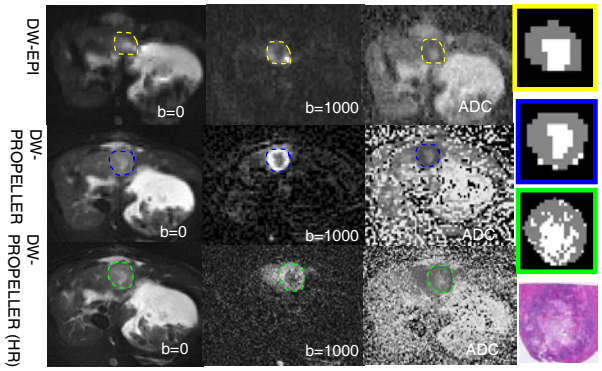



**Fig 3.** DWIs and corresponding ADC maps of a representative tumor slice acquired using DW-EPI, DW-PROPELLER and high resolution DW-PROPELLER. Tumor ROIs (dashed line) were classified based on the ADC value of each voxel. Classified ADC maps (last column) corresponded well the H&E slide. DW-PROPELLER (HR) improved characterization of intratumoral heterogeneity.

## Conclusions

DWI is a promising method for quantification of *in vivo* liver tumor necrosis in the VX2 tumor model. Multi-shot DW-PROPELLER provided superior image quality and more accurate tumor tissue characterization. Quantitative tumor necrosis measurements may permit earlier and more accurate therapy response assessments compared to the conventional size criteria. DW-PROPELLER may also offer the potential for high resolution DWI. Future studies will evaluate DWI-based tumor necrotic fraction measurements for accurate and early assessment of tumor therapy response in both animal models and cancer patients.

**Reference**: [1] Takahara et al. Radiat Med. 2004;22(4):275-82 [2]. Deng et al. Invest Radiol. 2006;41(4):410-4 [3]. Carano et a MRM. 2004;51(3):542-51 [4]. Deng et al. JVIR. Radiol. 2006;17(7):1195-200 [5]. Lyng et al. MRM. 2000;43(6):828-36 [6]. Pipe et al. MRM. 2002;47(1):42-52.