

# A quantitative MRI multi-parametric assay of colorectal cancer in APC<sup>Δ468</sup> mice

Zhuoli Zhang<sup>1</sup>, Weiguo Li<sup>1</sup>, Nichole R Blatner<sup>2</sup>, Kristen Dennis<sup>2</sup>, Daniele Prociassi<sup>1</sup>, Khashayarsha Khazaie<sup>2,3</sup>, and Andrew C Larson<sup>1,4</sup>

<sup>1</sup>Radiology, Northwestern University, Chicago, IL, United States, <sup>2</sup>Medicine, Northwestern University, Chicago, IL, United States, <sup>3</sup>R. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, United States, <sup>4</sup>Biomedical Engineering, Northwestern University, Evanston, IL, United States

## Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers in the western world [1]. New therapeutic strategies have improved survival rates for CRC patients however long-term outcome remains unsatisfactory. Transgenic mouse models of human cancer provide a powerful tool for identifying and testing clinically relevant therapeutic actions. The mouse model of hereditary intestinal cancer based on haploinsufficiency of the adenomatous polyposis coli gene (APC<sup>Δ468</sup>) has been widely validated for studying the pathophysiology and carcinogenesis of human disease in pre-clinical research settings [2]. By providing a organ specific (colon) tumor it offers the opportunity to test new therapies and observe tumor progression and response in a “realistic” tissue microenvironment. Non invasive imaging strategies are necessary to fully characterize the natural progression of the cancer as well as its response to therapy. In this study, we investigated the ability to use MR techniques to 1) rapidly and reliably detect colorectal tumors in the transgenic APC<sup>Δ468</sup> mouse model and 2) identify tumor-specific and potentially therapeutically relevant imaging biomarkers.

## Methods and Materials

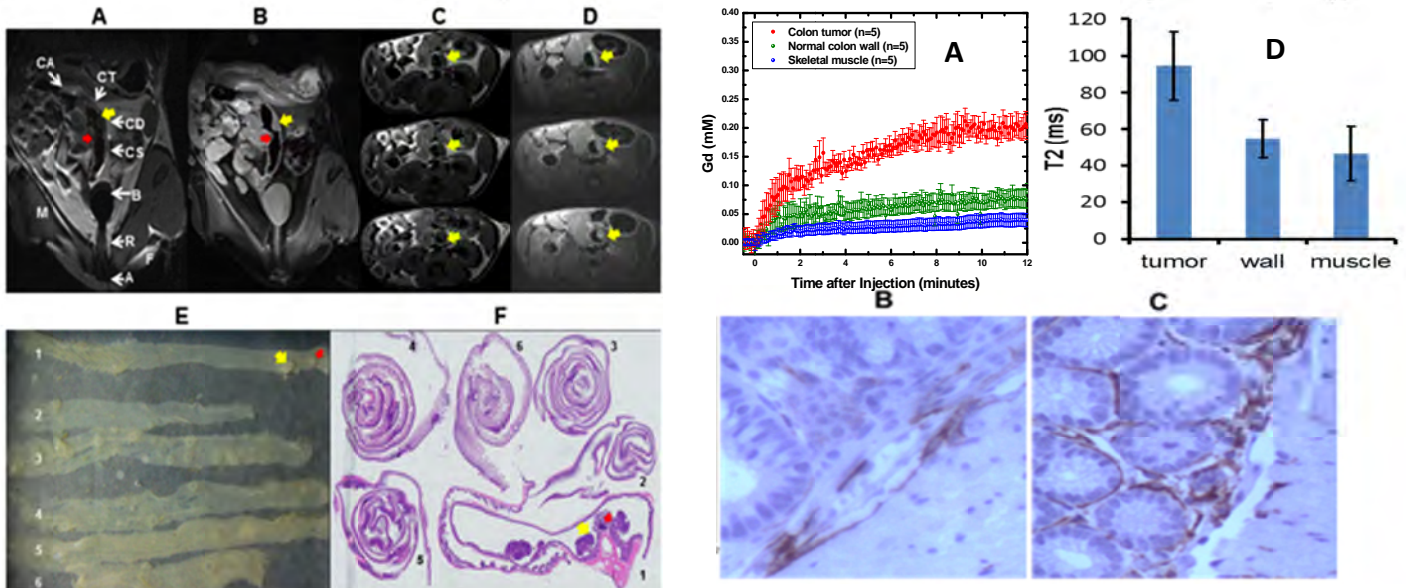
APC<sup>Δ468</sup> (4-5 months of age) mice were used for the study. MR measurements were performed on a Bruker ClinScan 7.0T small animal imaging system. T<sub>1</sub>-weighted (T<sub>1</sub>W) images, T<sub>2</sub>-weighted (T<sub>2</sub>W) images, and T<sub>2</sub> maps of the mouse abdomen and pelvic cavity were acquired in both coronal and axial orientations using GRE and TSE sequences. Individual tumor nodules were first identified on both T<sub>1</sub>W and T<sub>2</sub>W by an experienced imaging scientist (Z.Z.) and images and regions of interest were drawn around these areas. The corresponding T<sub>2</sub> values were plotted for three different tissue types : tumor (T), colon wall (CW) and skeletal muscle (M). Dynamic contrast-enhanced (DCE) measurements were performed using a series of T<sub>1</sub>W gradient echo images acquired with ~ 5 sec temporal resolution. Gaudolinium contrast agent (Prohance, BRACCO) was administered using a preinserted tail-vein catheter 3 minutes after beginning of the scan sequence. Temporal dependent quantitative estimates of tissue contrast agent concentration was plotted for the whole duration of experiment (~12 minutes). The initial area under the curve (IAUC 60 and 120 seconds post-contrast) measurements for the corresponding contrast curves was calculated for the normal CW, for T and for SM.

## Results

T<sub>1</sub>W and T<sub>2</sub>W MRM and necropsy samples (Fig 1A-F) were compared across a distance of ~ 3 cm from the rectum to splenic flexure. A total of 28 tumors were detected in the 10 APC<sup>Δ468</sup> mice using MRI, whereas 29 tumors were found within corresponding colon tissue samples examined at gross necropsy. Fig. 2A shows Gd tissue concentration versus time for T,CW and SM. DCE IAUC values (values not shown here) were significantly larger in tumors compared to both normal intestinal wall and skeletal muscle tissues (P<0.001). DCE measurements were concordant with corresponding post-necropsy immunostaining measurements demonstrating increased microvessel densities within the colon tumor tissues (Fig 2B,C). Fig 2D shows the average T<sub>2</sub> values for different tissues considered. Significant difference was observed between tumor, skeletal muscle, and normal intestinal wall tissues (P<0.05).

## Discussion

The use of a MR non invasive assay of tumor tissue pathophysiology has been validated histologically for the colorectal cancer mouse model APC<sup>Δ468</sup>. The protocol allows in vivo characterization of local tumor tissue embedded within healthy tissue of the colon and provides a set of quantitative biomarkers (T<sub>2</sub> values , IAUC, Time to peak ) which are being currently used to monitor longitudinal changes following therapy.



**Fig 1** Representative Anatomic T1W (A) and T2W (B) MR images in one of the *Apc*<sup>Min/+</sup> (Min) mouse (red and yellow arrows indicate tumors) . Axial T1W (C) and T2W (D) images of same tumors. (E); six segments were opened longitudinally for examination (arrows indicate the tumors). H&E of the 6 intestinal tract sections (F)

**Fig 2** In vivo CA concentration vs time curves (A). Representative slides show increased factor VIII antigen staining in tumor tissues (B) compared to adjacent normal wall tissues (C). Measured T<sub>2</sub> values

[1] Sifri R, Wender R, Lieberman D, et al. Developing a quality screening colonoscopy referral system in primary care practice: a report from the national colorectal cancer roundtable. *Cancer J Clin.* 2010;60:40-9.[2] Kwong LN, Dove WF. APC and its modifiers in colon cancer. *Adv Exp Med Biol.* 2009;656:85-106.