Early Detection of Prostate Neoplasm Using Pixel-by-pixel R1 Mapping Following Gd(ABE-DTTA) Administration in TRAMP Mice.

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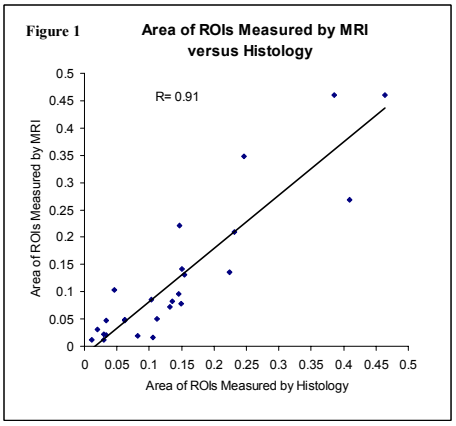
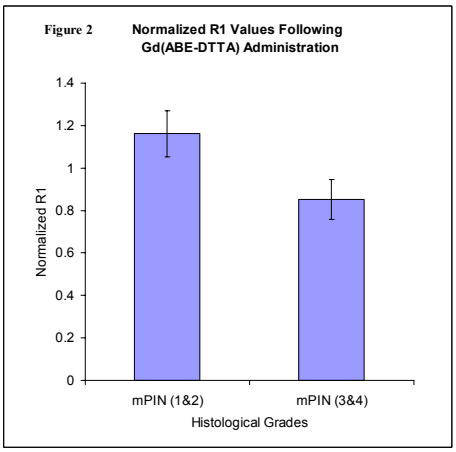
INTRODUCTION: Prostate cancer is the third most common cancer accounting for 5.7% of cancer deaths in the male population of the U.S. [1]. The factors responsible for the progression of localized, microscopic prostate cancers to a more aggressive form are poorly understood. Early detection of prostate cancer would be highly desirable, but unfortunately the detection rate with foci smaller than 5 mm is poor [2]. Our study was carried out in a TRAnsgenic Mouse model of Prostate cancer (TRAMP) (n=3) produced by Greenberg and colleagues who used a construct consisting of the Sv40 T antigen regulated by the same rat probasin gene promoter [3] [4]. TRAMP mice develop progressive forms of prostate cancer ranging from mPIN 1 to poorly differentiated prostatic adenocarcinoma. In our study, pixel-by-pixel R1 mapping of the prostate was carried out following Gd(ABE-DTTA) [5] administration. In the R1 map we could differentiate healthy areas from neoplastic islands with different histological grades in the prostate gland.

METHODS: After anesthesia induced by Isoflurane, 0.05 mmol/kg-body weight Gd(ABE-DTTA) was injected into the tail vein. MRI was carried out on a Bruker Biospec 4.7, equipped with a custom-made body coil of 78 mm diameter. Following the determination of the exact position of the prostate, a 2 mm tomographic slice, angulated on the urethra (and therefore through the prostate) was selected. A Multi Slice Multi Echo inversion recovery sequence was used for acquisition with the following parameters: FOV: 5 cm, matrix: 128x128, voxel size: 0.39x0.39x2 mm, recycle time: 3000 ms. A series of 8 inversion times from 100 to 1000 ms was used to acquire images. These images were then used to create the R1 map. After euthanasia and the excision of the urogenital tract, the latter was fixed *en bloc* with formaldehyde. A 2 mm slice, corresponding to that of the R1 map, was selected and dyed by using the Gomori-trichrome method. Histological analysis was carried out in 5μm step sections. The microscopic sections were scanned and the areas with the different histological grades were measured. Regions of interest (ROIs) of tissue with the same mPIN grade were determined in the histological sections. Corresponding ROIs in the R1 maps delineated by their R1 values were also measured. The areas of the corresponding ROIs determined by histology and MRI were correlated (Fig. 1). The R1 value in each ROI was normalized to that measured in the muscle tissues in each individual mouse to account for possible variations among the mice in contrast agent uptake. The normalized R1values were correlated to the histological grade (Fig. 2).





RESULTS: Significant correlation was found between the areas of the ROIs differentiated by MRI, and those determined by histology (Fig. 1). The observed normalized R1 (±SD) values in areas with healthy and low grade mouse mPIN versus those observed in areas with high grade mPIN and adenocarcinoma are shown in Fig. 2.

CONCLUSIONS: R1 mapping following the administration of the contrast agent Gd(ABE-DTTA) was successfully used to differentiate areas with mPIN 1&2 from areas with mPIN 3&4, detecting prostate neoplasms smaller than 2 mm. This method can non-invasively differentiate among areas with different prostate histology grades in early phase of prostate cancer in the TRAMP mouse model.

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