The Impact of Intermixed Normal Peripheral Zone elements on the Measurement of Apparent Diffusion Coefficient and T2 in Prostate Cancers

D. L. Langer[1,2], T. H. van der Kwast[3,4], A. J. Evans[3], L. Sun[5], M. J. Yaffe[5,6], J. Trachtenberg[7], and M. A. Haider[1,2]

[1]Medical Imaging, University Health Network, Toronto, Ontario, Canada, [2]Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada, [3]Pathology, University Health Network, Toronto, Ontario, Canada, [4]Pathology, Mount Sinai Hospital, Toronto, Ontario, Canada, [5]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, [6]Medical Biophysics, University of Toronto, Toronto, Ontario, Canada, [7]University Health Network, Toronto, Ontario, Canada

Introduction To guide focal therapy of prostate cancer (PCa), it is important that imaging methods accurately define tumor boundaries. Tumor location and extent may also contribute to the choice of active or deferred treatment. Maps of apparent diffusion coefficient (ADC), derived from diffusion weighted imaging (DWI), and quantitative T2 have been shown to differentiate tumor from normal peripheral zone (PZ) [1,2], and to improve PCa localization [3,4]. The mixture of normal tissues with malignant glands inherent in PCa may reduce contrast between normal PZ and tumors, potentially diminishing the ability to define lesions. The impact of tumor tissue heterogeneity on MRI has been briefly mentioned [5,6]; however, to date it has not been studied directly. We have investigated ADC and T2 in cancers containing a high proportion of normal PZ, versus dense cancers populated with malignant glands and reactive stroma.

Purpose To determine the impact of intermixed normal PZ elements within cancers on ADC and T2 measurements.

Materials and Methods

Eighteen men with known PCa underwent endorectal MRI on a 1.5T GE Excite HD platform prior to prostatectomy. Ethics board approval and informed consent were obtained. T2-weighted fast spin-echo (FSE) images were acquired, followed by DWI (DWI: TR/TE = 4000/77ms, matrix = 128x256, NEX = 10, FOV = 14cm, b = 0,600) and multi-echo FSE imaging (TR = 2000ms, 10 echo times (9.0-90.0ms), matrix = 256x128, NEX = 0.5, FOV = 20cm). All slice thicknesses were 3 mm, and all phase encoding was left to right. ADC and T2 maps were generated. Hematoxylin and eosin (H&E) stained whole mount sections were prepared at 3 mm increments, matching the *in vivo* MRI orientation [7]. Cancers arising in PZ tissue were delineated on each whole mount section if they were >3mm in diameter and were of Gleason pattern >=3. For each cancer focus, the section containing the largest malignant region was assessed regionally by a pathologist. A region of interest (ROI) in normal PZ tissue was delineated. The tumor was evaluated, and contiguous regions > 2mm x 2mm, primarily composed (>60%) of normal PZ tissue, were identified. Cancers were classified as 'sparse' if >50% of their surface area was comprised of these regions and 'dense' if >50% of the area was primarily malignant, fibrous or smooth muscle tissue. The MRI location of the whole mount section was determined by comparing internal histologic features with *ex vivo* and *in vivo* MRI. The tumor and normal PZ ROIs were drawn on the ADC and T2 maps by an experienced radiologist, blinded to the classification of each cancer. The median of each ROI was calculated. Population differences between normal PZ, sparse cancer, and dense cancer values were evaluated. Intra-patient differences between normal and malignant PZ was investigated by looking at matched-pair absolute signal differences as well as contrast, defined as the ratio of tumor to normal. Non-parametric tests were used for all analyses.

Results and Discussion

Twenty-eight cancers from eighteen patients were reviewed. Ten were classified as sparse, and eighteen classified as dense. Sample ROIs from pathology, ADC and T2 maps are shown in Fig. 1. Distributions of median values for all normal PZ, sparse cancer and dense cancer ROIs for ADC and T2 are displayed in Fig. 2. Tumor to normal contrast measurements are displayed in Fig. 3. For both ADC and T2, there were significant differences among the groups (ADC: p = 0.0001, T2: p = 0.005). ADC measurements of normal PZ and sparse cancer were significantly higher than dense cancer. T2 measurements of normal PZ were significantly higher than dense cancer. There were no significant differences between normal PZ and sparse cancer measurements for both ADC and T2. Matched-pair analysis of absolute differences between tumor and normal indicated no significant difference between normal PZ and sparse cancer (ADC: p = 0.94, T2: p = 0.92), however normal PZ was significantly higher than dense cancer (ADC: p = 0.0002, T2: p = 0.001). Contrast for dense cancers was statistically significantly different from sparse camcers (ADC: p = 0.008, T2: p = 0.009). By all measures, sparse cancers were indistinguishable from normal PZ. In our cohort, dense cancers were approximately twice as likely to occur compared to sparse cancers (18 versus 10); however, 7 of the 18 dense cancers had sparse regions making up 15-30% of their surface area. This implies that there may be intrinsic limitations to PCa detection and delineation using ADC and T2. Due to the small patient cohort, this study was limited to PZ cancers, and does not address heterogeneity in central gland malignancies or benign pathologies. However, as the majority of PCa arises in PZ tissue, the impact of these findings for routine clinical practice is significant.

Conclusion

This study demonstrates that the presence of normal PZ tissues in PCa impacts ADC and quantitative T2 values. Dense cancers are significantly different from normal PZ; however, sparse cancers, with a high component of normal tissues, are indistinguishable from the surrounding normal PZ.

References [1] Gibbs *et al*, MRM 2001; 46:1054-1058. [2] Hosseinzadeh and Schwarz, JMRI 2004; 20:654-661. [3] Haider *et al*, AJR 2007; 189:323-328. [4] de Souza *et al*, Br J Radiol 2007; 80:90-95. [5] Quint *et al*, Radiology 1991; 179:837-842. [6] Schiebler *et al*, Radiology 1989; 172:131-137. [7] Langer *et al*, Proc. Intl. Soc. Mag. Reson. Med. Berlin 2007, 747.

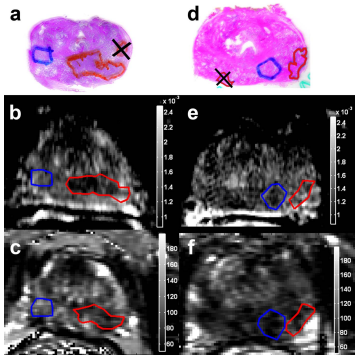

Figure 1. Regions of interest (ROIs) for pathology and imaging for dense (**a**,**b**,**c**) and sparse (**d**,**e**,**f**) cancers. Normal (blue) and tumor (red) tissues are drawn on H&E sections (**a,d**), and transferred to axial-oblique ADC (mm/s^2) (**b,e**) and T2 (ms) (**c,f**) maps. The lesion crossed-out in **a** did not meet size criteria for evaluation, and in **d** the crossed-out lesion was evaluated in another section where the diameter was greater.

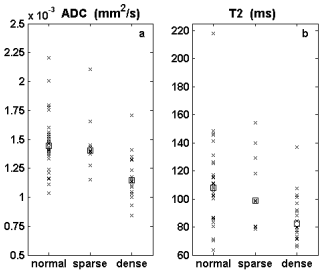

Figure 2. Distributions of median values from all regions of interest, all tissue types. At least one of the groups was found to have a significantly different median in both ADC measurements (**a**, p = 0.0001) and T2 (**b**, p = 0.005). For both ADC and T2, dense cancers were significantly lower than normal PZ and there was no statistical difference between normal PZ and sparse cancers. Median values from each ROI are shown by each '**x**,' and the medians of the distributions are plotted as '□'.

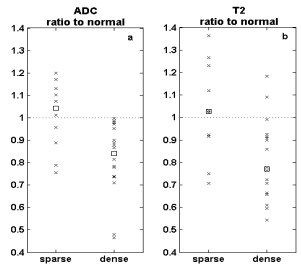

Figure 3. Contrast Ratios (cancer/normal). For both ADC (**a**) and T2 (**b**), there is a statistically significant difference between sparse and dense cancer populations, p = 0.008 and p = 0.009 respectively. The median value from each normalized ROI is shown by each '**x**,' and the medians of the distributions are plotted as '□'.