Dynamic contrast enhanced MR imaging for the assessment of prostate cancer aggressiveness at 3T

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INTRODUCTION: Prostate cancer (PCa) is the most common malignancy in the Western male population with an incidence of 648,000 and the third leading cause of death in developed countries in 2008 (1). Since not all prostate cancers are life-threatening, an accurate assessment of aggressiveness is essential to prevent overtreatment of indolent cancers. MRI plays an upcoming role in the diagnosis and management of prostate cancer. Next to T2-weighted imaging for detailed anatomical information (2), functional MRI techniques such as Diffusion Weighted Imaging and MR spectroscopic imaging have potential to assess aggressiveness (3;4;5). Dynamic contrast enhanced (DCE) MR imaging has already provided its usefulness in detecting and staging of prostate cancer (6;7). The purpose of this study is to retrospectively validate the performance of pharmacokinetic parameters derived from dynamic contrast enhanced MRI of the prostate at 3T for assessing PCa aggressiveness, with Gleason scores of cancer foci of whole mount section histopathology of resected prostates as the gold standard.

METHODS: The need for informed consent for retrospective use of anonymized clinical data was waived by the institutional review board. Fifty-three patients with histologically proven PCa who underwent multiparametric MR imaging with the use of an endorectal coil at 3T were enrolled in this study before prostatectomy. DCE-images were acquired by using turboflash 3D spoiled gradient echo images with a high temporal resolution, TR 2.4 or 2.9, TE 1.35 or 1.51, flip angle 14 or 10 and slice thickness 3 or 4 mm during a 15mL i.v. bolus injection of a gadolinium chelate (Dotarem®, Guerbet), which was administered with a power injector (Spectris Solaris, Medrad) and followed by a 20mL saline flush. For each patient a region of interest (ROI) was drawn within an area of PCa and a separate ROI was drawn within a non-cancer part of the peripheral zone (PZ) by a radiologist in consensus with a urogenital pathologist, based on the prostatectomy specimens (see fig.1). Calibration of the pharmacokinetic modeling was performed by using a ROI with histologically proven non-cancer PZ tissue as reference tissue to estimate the patient-dependent arterial input function in a method described earlier (8;9). Care was taken to choose the non-cancer tissue for calibration in a non-enhancing homogeneous area, excluding for example peri-prostatic blood vessels. For each ROI the mean, 25th and 75th percentile of the semi-quantitative parameters LateWash (Washout) and Relative Enhancement (RelEnh, signal intensity of peak enhancement divided by signal intensity at start of enhancement) were determined, as well as for the pharmacokinetic parameters K^{trans}, K_{ep} and V_e (10). PCas were classified as low grade if they consisted only of Gleason grades (GG) 2 or 3, as intermediate grade with a secondary or tertiary GG of 4 but no 5 component, and as high grade with a primary GG of 4 and/or 5 as a primary/secondary or tertiary score. All parameters were correlated with the three aggressiveness classes and with non-cancer prostate tissue. Statistical analyses were performed using the Kruskal-Wallis (KW) test in combination with the Dunn's Multiple Comparison test for all aggressiveness classes including non-cancer tissue, and a Mann Whitney (MW) test between separate aggressiveness classes. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS: Two patients had to be excluded because their prostate did not contain non-cancer PZ tissue. The remaining 51 patients had a total of 63 relevant PCa foci (with a minimum volume of 0.5cc), whereof 45 in the PZ, 16 in the transition zone (TZ) and two covering both zones. The ROIs covering both zones were excluded from analysis. In the PZ there were 18, 12 and 16 PCa foci for the low, intermediate and high grade classes, respectively. In the TZ the number of PCa foci were 6, 2 and 8 for the low, intermediate and high grade classes, respectively. No significant differences were found for the pharmacokinetic parameters K^{trans}, K_{ep} and V_e between the different aggressiveness classes in both PZ and TZ. However, for K^{trans}, K_{ep} and V_e there was a significant difference between means of non-cancer PZ versus all PZ cancers (p<0.0001, p=0.0003 and p<0.0001 respectively, MW). For LateWash in the PZ there was a significant difference between the mean of low versus high aggressiveness, between low and combined intermediate/high aggressiveness and between high aggressiveness and combined intermediate/low aggressiveness, see fig 2 (all p<0.05, MW). RelEnh showed a significant difference for the mean between non-cancer tissue and prostate cancer in the PZ (p<0.0001, MW). The 75th percentile of RelEnh showed a significant difference between low and high aggressiveness classes in the PZ (fig. 2), between low and combined intermediate/high aggressiveness, and between high and combined intermediate/low aggressiveness, all with a p-value of <0.05 (MW).

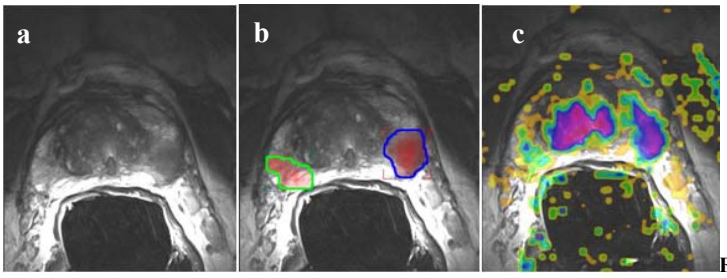
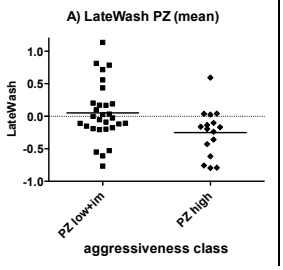


Fig.1



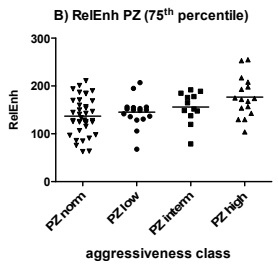


Fig.2

Fig.1. *Axial T2-w MRI of the prostate of a 65-year-old man with Gleason 4+5 PCa (=highly aggressive). a) T2-weighted image with PCa in the left PZ, b) ROI in blue line covering PCa, ROI in green line covering non-cancer tissue of the PZ, c) K^{trans} overlay on T2-weighted image, enhancement of the PCa region in the left PZ and less enhancement of non-cancer prostate tissue.* ***Fig. 2.*** *Non-cancer tissue parameters for a) LateWash (mean) low aggressive PCa and combined intermediate/ high aggressive PCa, b) Relative Enhancement (75th percentile) low aggressive PCa, intermediate aggressive PCa and high aggressive PCa.*

DISCUSSION: For quantitative parameters our results were similar to previous reports showing higher K^{trans}, K_{ep} and V_e in prostate cancer of the PZ compared to non-cancer prostate tissue. However, these parameters did not show a significant correlation with aggressiveness. According to the literature, there may be a correlation between microvessel density (MVD) and PCa aggressiveness, which could indicate that a lack of significance for DCE and PCa aggressiveness is inherent to a failure of the pharmacokinetic model; however, the current consensus about MVD is that it should not be implemented in routinely performed pathology reports due to for example different scoring techniques and inter-observer variability (11;12). Therefore we cannot make the assumption that the lack of correlation is model-based. The semi-quantitative parameters LateWash and RelEnh showed a correlation with aggressiveness in the PZ for low and high aggressive PCa, but with considerable overlap between the different classes. Since other functional MR techniques also showed potential to assess aggressiveness with considerable overlap, a next step would be to combine these techniques to investigate their complementary value. In the TZ there was no correlation between aggressiveness classes for any of the parameters, probably due to the low number of lesions.

CONCLUSION: In this retrospective study we found that the semi-quantitative parameters LateWash and Relative Enhancement may be feasible measures to assess the aggressiveness of PCa in the PZ, although due to the overlap between distinct classes further research is needed. Pharmacokinetic parameters K^{trans}, K_{ep} and V_e proved its usefulness for detection of PCa in the PZ, however, for the assessment of aggressiveness this study does not show any value in these parameters thus far. The future combination with other functional MR techniques might improve the distinction between the aggressiveness classes.

Rerefences: (1) Jemal A et al, CA Cancer J Clin 2011 (2) Fütterer JJ et al, Top Magn Reson Imag 2008 (3) Verma S et al, AJR 2011 (4) Kobus T et al, Eur Urol 2011 (5) Hambrock T et al, Radiology 2011 (6) Franiel T et al, Eur Radiol 2011 (7) Langer D et al, Radiology 2010 (8) Huisman HJ et al, JMRI 2001 (9) Kovar DA et al, JMRI 1998 (10) Tofts PS et al, JMRI 1999 (11) Ebersdobler A, World J Urol 2010 (12) Botswick DG, Arch Pathol Lab Med 2000
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