Prostate Cancer localization with a Multiparametric MR Approach (PCaMAP): initial results of a multi-center study

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Introduction

The primary objective of the multi-center trial PCaMAP (NCT01138527) is to prove the diagnostic accuracy of 3T multi-parametric MR imaging (mpMRI) in distinguishing clinically significant prostate cancer from other prostate tissue, with whole-mount section histopathology of resected prostates as the gold standard. The MR protocol consists of high resolution T_2-weighted imaging, diffusion weighted imaging (DWI), dynamic contrast enhanced (DCE) imaging and ^{1}H-spectroscopic imaging (MRSI) at 3T without an endorectal coil (ERC). Here we present initial results of the validation part of this study.

Methods

Thirty-eight patients from 4 institutions were consecutively included (mean age 62 y, mean PSA 7.7 ng/ml, biopsy Gleason score [GS] range 6–8). All scans were performed using identical MRI protocols on 3T MRI systems (Siemens Healthcare, Erlangen) using the external body and spine array coils for signal reception. High-resolution T_2-weighted imaging was performed in three orthogonal directions. DWI was performed using *b*-values of 0, 100, 400, 800 s/mm^2, and ADC maps were calculated using all b-values. 3D MRSI was performed with a PRESS sequence [1]. Spectra were automatically phased and fitted using Syngo.Via (Siemens Healthcare), accounting for contributions of choline (Cho), creatine (Cr) and citrate (Ci). Gd-enhanced DCE data were acquired using a T_1-weighted TWIST sequence (time resolution 4s) and processed using the Tissue4D package (Siemens Healthcare). This yielded maps of K^{trans}, k_{ep}, v_e using a two-compartment Tofts model and a population based arterial input function (AIF), as well as the initial area under the enhancement curve (iAUC). Tumors were individually outlined and graded on histology slides according to a study-specific protocol [2]. Guided by histopathology and blinded to the spectra and any functional MR data, a spectroscopist in consensus with an experienced radiologist annotated spherical ROIs of the approximate true size of an MRSI voxel on the MRSI grid in non-cancer peripheral zone (PZ), non-cancer central gland (combined central and transition zones, CG), and tumors with a volume >0.5 cc (PCa) [3]. Two spectroscopists independently checked the spectral quality in each annotated ROI. The (Cho+Cr)/Cit ratio (CC/C), the Cho/Cr ratio (C/C), the 25th percentile of ADC values and the medians of K^{trans}, k_{ep}, v_e and iAUC were calculated for each ROI. The fraction of the total variance attributable to differences between institutions (f_v) was quantified for each parameter using a restricted maximum likelihood variance components estimation, which included 'institution' and 'patient' as random main effects. Differences between parameter values in PCa, PZ and CG tissue were assessed using Kruskal-Wallis tests with Dunn's post tests to account for multiple comparisons. A *p*-value <0.05 was considered statistically significant.

Results

A total of 315 ROIs were annotated, of which 104 were in prostate cancer (8 GS≤5, 32 GS=6, and 64 GS≥7). MRSI fits were approved by both readers in 51% of ROIs in non-cancer (NC) tissue and 47% in PCa, with substantial agreement between observers ($\kappa = 0.76$). The approval rate was similar in 3 out of 4 sites (~60%), but considerably lower in one site (Site 4, ~20%). Differences between institutions accounted for an average of 9% of the total variance in each parameter in PZ (maximum: 25% for CC/C), see Fig 1. In the CG, the average was 12% (maximum 34% for CC/C). Significant differences in median parameter values were observed between PCa and PZ for ADC, CC/C, iAUC (all $p \leq 0.001$), C/C, K^{trans} and v_e (all $p \leq 0.01$), but not for k_{ep}. Between PCa and CG, significant differences were observed for ADC, k_{ep} (both $p \leq 0.001$), C/C, K^{trans} and iAUC (all $p \leq 0.01$), but not for CC/C and v_e. However, overlap between PCa and NC tissues was considerable, especially for MRSI and DCE parameters (Fig 2).

Discussion

Data homogeneity across different centers is important in the validation of multi-center mpMRI. We showed that overall, site-specific variations were small compared to inter-patient and random variations in NC tissues, indicating that identical MRI protocols can provide quantitatively homogenous data. MRSI data inhomogeneity depends in part on the site, reflecting differences in local expertise. Quantitative mpMRI parameters showed a higher degree of overlap between PCa and NC tissue than reported in single site studies [4–6]. In both MRSI and DCE, alternative post-processing protocols (e.g., including personalized AIFs in DCE) are being investigated to improve separation between PCa and NC tissues. Before making predictive assessments of new cases, the best strategy to combine these parameters needs to be established.

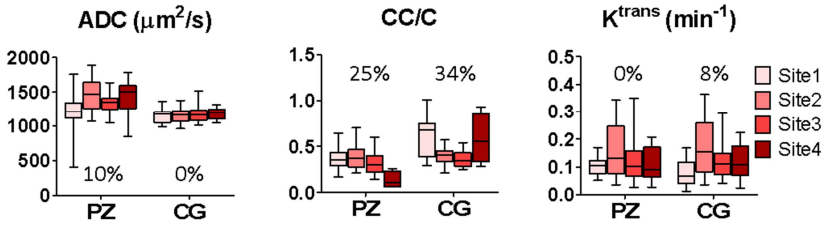

Fig. 1: Examples of quantification of the fraction of the total variance attributable to differences between institutions (f_v) in non-cancer tissue. Percentage values of f_v for these examples are indicated in the graphs.

Conclusions

Multi-center mpMRI with identical protocols at 3T without ERC provides homogeneous quantitative parameters for NC tissues, and can detect differences between PCa and NC tissues. Additional steps are needed to improve separation between these tissues. The validation part of this prospective trial will be used to determine the parameters contributing most to the detection and localization of clinically significant PCa as well as their optimal cutoff values.

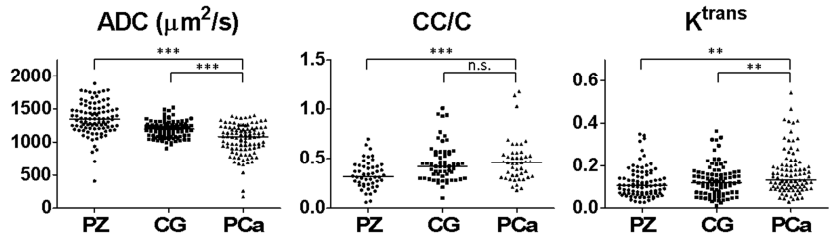

*Fig. 2: Examples of combined multi-center DWI, MRSI and DCE data showing significant differences between PCa and NC tissues. ***: p≤0.001, **: p≤0.01, n.s.: not significant.*

References

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Acknowledgements: ERC Grant agreement n° [243115], Siemens Healthcare for research support and providing Syngo.Via, the PCaMAP consortium for collaborative support.