Discriminating low-grade from high-grade peripheral zone prostate cancer by multiparametric MRI: a multicenter study

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Introduction

Non-invasive assessment of prostate cancer grade is of great clinical importance for selecting and following-up patients for active surveillance with a minimum number of biopsies. All three imaging methods commonly employed in prostate multiparametric MRI (mpMRI), i.e. diffusion weighted imaging (DWI), ^{1}H MR spectroscopic imaging (^{1}H-MRSI) and dynamic contrast enhanced (DCE) imaging have been shown to correlate with Gleason scores. However, these correlations have to date not been explored in a multi-institutional setting, and no studies combining all three methods have been published. Here we present initial results for peripheral zone (PZ) prostate cancers in a multi-center study encompassing all 3 methods, using whole-mount section histopathology of resected prostates as the gold standard.

Methods

Fifty patients from 5 institutions (12, 10, 10, 10 and 8 patients) were included (mean±SD age 61±7y, PSA 7.4±3.5 ng/ml, Gleason score [GS] range 5-9). All centers used identical scanning protocols on 3T MRI systems (Siemens Healthcare, Erlangen) using external body and spine array coils. High-resolution T_2-weighted imaging was performed in three orthogonal directions, and DWI, 3D MRSI and DCE were acquired with identical protocols at all centers[1]. ADC maps were calculated from the DWI data using the scanner software (version VB17). MRSI data were quality checked and fitted accounting for contributions of choline (Cho), spermine (Spm), creatine (Cr) and citrate (Ci) using LCModel[2]. Ratios of (Choline+Spermine+Creatine)/Citrate (CSC/C) and Choline/(Spermine+Creatine) (C/SC) were calculated. DCE data were fitted with a semi-quantitative model yielding parameter maps of the initial area under the enhancement curve (iAUC), relative enhancement (RE), washin (WI), and washout (WO) using in-house developed software. Tumors were outlined and graded on histology slides according to a study-specific protocol[3]. Guided by histology and blinded to any functional imaging results, ROIs were drawn on T2w images in prostate cancer regions (volume >0.5 cc). Each ROI consisted of a central MRSI voxel and up to six directly neighboring MRSI voxels, provided they were located in the same tissue[1]. To correlate MRSI data with DWI and DCE, each MRSI voxel was represented by a sphere of its approximate true size (1.0 cc). Spheres were trimmed so as to contain only the tissue of interest. For each MRSI voxel/sphere the following quantities were calculated: 25th percentile (25p) for ADC, 75p for iAUC, RE and WI, and 25p for WO. The most deviating value of each parameter in each multi-MRSI-voxel ROI was used for further analysis. Tumors were stratified into low (L), intermediate (I) and high-grade (H) classes[4]. Spearman's correlation coefficients were calculated, and differences between low-grade and combined intermediate and high-grade tumors were assessed using mixed model analysis and ROC analysis with patient-level bootstrapping to account for within-patient correlations. The performance of combinations of parameters was analyzed using Logistic Regression modeling (LRM).

Results

A total of 45 PZ tumors from 39 patients with volume >0.5cc on histopathology and known GS were analyzed (L: 11, I: 16, H: 18), and 87 ROIs were annotated (average 5.2 MRSI voxels per ROI). Significant associations between tumor grade and parameter values were found for ADC, CSC/C and WI (Fig 1, Table 1). Significant differences between L and I+H cancers were found for ADC and CSC/C (Table 1). ROC analysis of these parameters resulted in areas under the curve (AUCs) of 0.80 ± 0.13 and 0.70 ± 0.19. A standardized threshold approach[5] (STA) with a C/SC cutoff of 0.4 yielded an AUC of 0.74. A Logistic Regression Model (LRM) including ADC and the MRSI-derived STA score yielded a slight improvement over using ADC alone (AUC 0.83 ± 0.15).

Discussion

Non-invasive assessment of prostate cancer aggressiveness is of high clinical importance, minimizing the number of biopsy needles to select and following up patients in active surveillance regimens. Multiparametric MRI has shown promising results for this purpose[6]. However, mpMRI methods need to be further validated in multi-center studies. These results show for the first time that good separation between L and I+H PZ tumors can be achieved in a multi-center setting, particularly with ADC maps. AUCs achieved with ADC and CSC/C were comparable to those reported in a recent single-center 3T study with similar design[4]. DCE-derived parameters were outperformed by DWI and MRSI-derived parameters, and performed slightly worse than in a recent single-center study[7]. Although this may be improved using patient-specific calibration methods and/or pharmacokinetic modeling, such methods may also introduce additional uncertainties. Combining CSC/C with C/SC with a standardized threshold approach lead to slightly improved MRSI performance, but LRM only lead to a small additional value of MRSI over ADC alone for separating L from I+H, in concordance with a previous report[4]. However, it has been suggested that MRSI-derived parameters may be more indicative of aggressiveness than ADC for TZ tumors[4]. Although TZ data are also available in this study, the low number of tumors available in this zone have thus far precluded drawing solid conclusions.

Conclusions

Using identical scanning protocols at 3T without an ERC in a multi-center setting yields good separation between low-grade and higher-grade tumor tissues with ADC maps.

References

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*Table 1: Statistical analysis. LMM: Linear mixed model. L: low-grade; I: intermediate grade; H: high-grade. *: p<0.05, **: p<0.01, ***: p<0.001, ns: not significant*

	Spearman's correlation		LMM L vs I+H	ROC analysis L vs I+H	
	r	p	p	AUC	p
ADC	-0.53	***	***	0.80 ± 0.13	***
CSC/C	0.42	***	*	0.70 ± 0.19	**
C/SC	0.10	ns	ns	0.58 ± 0.18	ns
iAUC	0.18	ns	ns	0.65 ± 0.24	ns
Rel.Enh.	0.10	ns	ns	0.61 ± 0.32	ns
WashIn	0.23	*	ns	0.63 ± 0.30	ns
WashOut	-0.09	ns	ns	0.58 ± 0.24	ns
LRM	--	--	***	0.83 ± 0.15	***

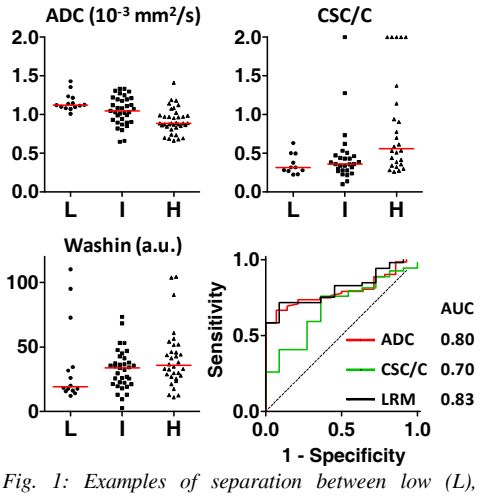

Fig. 1: Examples of separation between low (L), intermediate (I) and high (H) grade PZ tumors for ADC (a), CSC/C (b) and iAUC (c). d: ROC curves for L vs I+H for ADC (red), CSC/C (green) and a logistic regression model (LRM) including ADC and the MRSI-derived STA score (black).