Stratification of disease aggressiveness of prostate cancer using MRSI and DWI

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Introduction: Current challenge to clinicians is the identification of men with low risk prostate cancer (PCa) compared to high risk disease for better treatment selection. Serum prostate specific antigen (PSA) in combination with digital rectal examination (DRE) and transrectal ultrasound (TRUS) guided biopsy is used for PCa diagnosis. Because of multifocal, heterogeneity nature of PCa, TRUS-guided biopsy misses cancer foci due to sampling errors. Moreover, PSA suffers from overdiagnosis of indolent tumors (1). Gleason score (GS) is a predictor of tumor aggressiveness that is obtained on TRUS guided biopsy. Hence, it is of prime importance to find some non-invasive tool which could strongly correlate with tumor aggressiveness. The quantitative parameters like metabolite ratio obtained using MRSI and apparent diffusion coefficient (ADC) using DWI seems to be promising for the evaluation of tumor aggressiveness. In the present study, we evaluated the pre-biopsy MRSI and DWI in order to stratify the tumor aggressiveness of PCa.

Materials and Methods: Between 2008 and 2011, a total number of 115 patients underwent pre-biopsy MR evaluations at 1.5 Tesla MR scanner (AVANTO, Siemens Health Care, Germany) using an endorectal surface coil (Medrad Inc., Pittsburgh, PA) in combination with a pelvic phased array coil. Patients [mean age (67.2 ± 7.4 yrs, range 55-85 yrs) and serum PSA (median = 8.59 ng/ml, range 4.0 - 794.0 ng/ml)] presented to the Urology clinic who were scheduled to undergo a standard 12 core TRUS-guided biopsy for PCa due to raised PSA or an abnormal DRE were recruited for this study. Following scout images, T1-weighted images in transverse plane and T2-weighted images in three orthogonal planes were acquired using turbo spin-echo sequence (TR = 5000 ms, TE = 98 ms, FOV = 280, matrix size = 256 × 256, slice thickness = 5 mm, without the interslice gap). The MRSI matrix was planned on transverse T2- weighted images. The parameters used for MRSI were as follows: TR = 1300 ms, TE = 120 ms, voxel size = 5 x 5 x 5 mm^3, averages = 3, total acquisition time = 17 min. Single shot EPI pulse sequence was used for diffusion weighted (DW) images. Slice positions of DWI were matched with T2-weighted images. Five different b values (0, 250, 500, 750 and 1000 s/mm^2) were used to acquire different diffusion-weighted images (TR = 3000 ms, TE = 96 ms, 5 mm slice thickness without interslice gap, number of averages = 2, bandwidth = 1500 Hz). A cut-off value of metabolite ratio [Citrate/(Choline+Creatine)] ratio < 1.2 and cut-off value of ADC < 1.17 $x10^{-3}$ mm^2/s were used to predict malignancy from our earlier study (2, 3). The study was approved by Institute ethics committee and all patients gave written signed informed consent. The ADC values and metabolite ratios were correlated with the biopsy findings. One-way analysis of variance (ANOVA) was used to determine whether there were any significant differences between the means of three GS groups (low risk PCa ≤ 6, intermediate risk PCa = 7, high risk PCa ≥ 8) and to observe the dependency of metabolite ratio and ADC values on GS. A p value of < 0.05 was considered as significant. All the statistical analyses were carried out using statistical software SPSS 16.

Results: A total of 115 men met the inclusion criteria and out of these 25 patients were detected positive for malignancy on TRUS biopsy (histopathology). Figures 1 and 2 show the "box and whisker"' plots of metabolite ratios and ADC values of various GS groups, respectively ($p < 0.05$). A summary of patient details, tumour characteristics, metabolite ratios and ADC values for various GS is provided in Table 1.Out of 25 patients, two patients had GS = 4 and were pooled with GS = 6 as low risk PCa. One patient had GS = 9 and was pooled with GS = 8 as high risk tumor. Post hoc analysis revealed that the metabolite ratio and ADC for three different grades of tumors was statistically significant ($p < 0.01$). A statistically significant difference in ADC vlaues was observed between GS = 6 and GS = 8 ($p < 0.01$) and between GS = 7 and GS = 8 ($p = 0.05$). However, no statistically significant difference was observed between GS = 6 and GS = 7 ($p = 0.19$) despite reduction in ADC. For metabolite ratios, statistically significant difference was observed between GS = 6 and GS = 7 ($p < 0.05$) as well between GS = 6 and GS = 8 ($p < 0.01$). However, for GS = 7 and GS = 8, the difference was not statistically significant ($p = 0.17$).

Discussion: The present study showed the reduction of metabolite ratios and ADC values with increased GS. GS of 6 and 7 were studied using MRSI and DWI in an earlier study by Nagarajan et al. (4); however the present study covers the full spectrum (low risk to high risk) of the disease aggressiveness. Gleason grade correlates with degree of cellularity, degree of glandular differentiation and stromal invasion in PCa. Because of the reduced extracellular space it is possible that significantly decreased ADC values were observed in higher GS group. In one patient with GS = 6, the calculated ADC value was 1.59 x 10^{-3} mm^2/s, which was false negative. In this patient, the pathology findings revealed that majority of tissues have high-grade prostatic intraepithelial neoplasia. Metabolite ratios were strongly correlated with the lesion GS and agrees with the previous study of Nagarajan *et al.* (5). A potential limitation of the current work is that we could not compare the GS on TRUS biopsy with GS on final histopathology of radical prostatectomy specimens as the outcome of both grading could differ (5). However, ours is pre-biopsy MR studies in such group of patients.

Conclusion: In conclusion, the results of the present study indicate that MRSI and DWI could stratify the PCa disease aggressiveness non-invasively. This study can guide clinicians to select proper treatment regimen.

References: (1) Schroder FH *et al. NEJM*. 2009; 360: 1320-8 (2) Kumar V *et al. NMR Biomed*. 2007; 20: 505-11 (3) Kumar V *et al. J Magn Reson Imaging* 2009; 30: 842-8 (4) Nagarajan R *et al. J Magn Reson Imaging* 2012; 36: 697-703 (5) Giusti S *et al. Abdom Imaging* 2010; 35: 757-63

No. of patients	115	
No. of PCa patients	25	
Ages (mean ± SD)	67.2 ± 7.4 yrs, range (55-85 yrs)	
Gleason scores	**Metabolite ratio [Cit/(Cho+Cr)] mean ± SD**	**ADC (x10^{-3} mm^2/s) mean ± SD**
Low risk (GS ≤ 6); n = 9	0.42 ± 0.11	1.06 ± 0.21
Intermediate risk (GS = 7); n = 10	0.24 ± 0.09	0.93 ± 0.09
High risk (GS ≥ 8); n = 6	0.14 ± 0.06	0.73 ± 0.06

Table 1: Patient details, tumour characteristics with mean metabolite ratios and ADC values

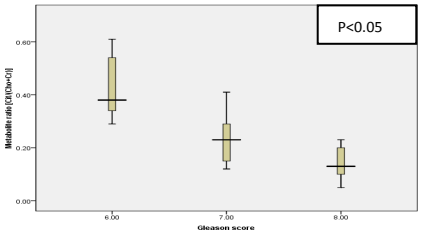

Fig. 1: Box plots of metabolite values of different GS groups

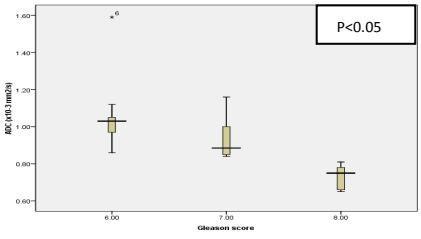

Fig. 2: Box plots of ADC values of different GS groups