Validation of multiparametric magnetic resonance imaging and spectroscopy (DWI/MRSI) to assess prostate cancer aggressiveness

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Introduction

Prostate cancer is the most common non-cutaneous cancer in men. Screening for prostate cancer by means of prostate specific antigen levels will not only lead to a reduced number of prostate cancer deaths, but also to overdiagnosis and overtreatment due to a high number of indolent cancers detected [1]. In order to give a patient optimal treatment, we need a method to discriminate indolent tumors from aggressive ones. A positive correlation was found between the Gleason score (GS) and the choline plus creatine over citrate ((Cho+Cr)/Cit) ratio using ^{1}H magnetic resonance spectroscopic imaging (^{1}H MRSI) [2,3]. A negative correlation was revealed between the GS or level of cell differentiation and the Apparent Diffusion Coefficient (ADC) measured with diffusion weighted imaging (DWI) [4,5]. However, both methods show (substantial) overlap between the different GS and the (Cho+Cr)/Cit ratio or ADC values. The aim of this study is to validate the individual and combined ^{1}H MRSI and DWI methods to discriminate between aggressive and indolent prostate cancers using histopathology as the gold standard.

Methods

37 patients with biopsy proven prostate cancer had a MRI/MRSI/DWI exam on a Siemens Trio 3T system using an endorectal coil and body-array coil. The MRSI data were measured with a PRESS sequence using outer volume suppression and Mescher Garwood dual-frequency water and lipid suppression [6]. DWI was performed with a single shot echo planar imaging sequence with diffusion-encoding gradients in three directions. The scanner software automatically calculated the ADC values from b-values of 0, 50, 500 and 800 s/mm^2. After the MR exam, prostatectomy was performed and a pathologist indicated the location and the GS of the tumors. The tumors were then divided in three aggressiveness classes: *low-grade*, consisting only of Gleason grades 2 and/or 3; *intermediate-grade*, secondary or tertiary Gleason grade of 4, but no 5 component; or *high-grade*, tumors with 4 as primary Gleason grade and/or a 5 component present.

A radiologist, blinded to the spectra, used the histopathology to assign all voxels belonging to a tumor on T2 weighted images with the voxel matrix of the spectroscopic exam overlaying the images. Metabolite Report (Siemens, Erlangen, Germany) was used for automated fitting of the spectra of these voxels and calculation of the (Cho + Cr)/Cit and Cho/Cr ratios. In the analysis only voxels were included that passed visual inspection for correct fit, phasing and minimum residuals by a spectroscopist. Polyamine signals were not separately fitted. Home-built software (MRCAD) was used to determine the median ADC value of tissue represented by a MRSI voxel. Around each selected voxel a sphere was drawn approximating the actual voxel size. Each sphere had to be completely within the prostate in order to have a representative ADC value and to be included in the analysis. The software calculated the median ADC value for each sphere.

The metabolic ratios and median ADC values were imported in MATLAB (MathWorks, Natick, MA) to perform the remainder of the analysis. 3 measures were calculated from all spheres and voxels belonging to a tumor: 1) the minimum of the median ADC values of all spheres; 2) the maximum (Cho + Cr)/Cit ratio of all voxels; and 3) the maximum Cho/Cr ratio of all voxels. Receiver operating characteristic (ROC) curves were made to analyze each measure's performance in discriminating low- and high-grade tumors and linear discriminant analysis (LDA) was used to classify tumors based on all three measures.

Results

45 clinically significant tumors in the peripheral zone (N=35) and central gland (N=10) were included of 36 patients. One patient was excluded because of misregistration between MRSI and DWI. The tumors were classified as following: 15 low-grade, 10 intermediate and 20 high-grade tumors. The area under the curve (AUC) of the ROC curves (Figure 2) for discriminating between low- and high-grade tumors was not significantly different for minimum ADC, maximum (Cho+Cr)/Cit and Cho/Cr as variable (Table 1). However, the sensitivity and specificity calculated from the optimal cut-off, which was determined from the ROC curves, is highest for the Cho/Cr ratio. Using all three measures to classify the tumors by means of LDA resulted in the highest sensitivity and specificity: The combination of both MRSI and DWI compared to the use of DWI alone, resulted in 4 additional patients correctly classified with a high-grade tumor instead of low grade. This difference is smaller when comparing with the Cho/Cr ratio: one extra patient that was misclassified as low-grade by the Cho/Cr ratio is classified as high-grade in the LDA analysis.
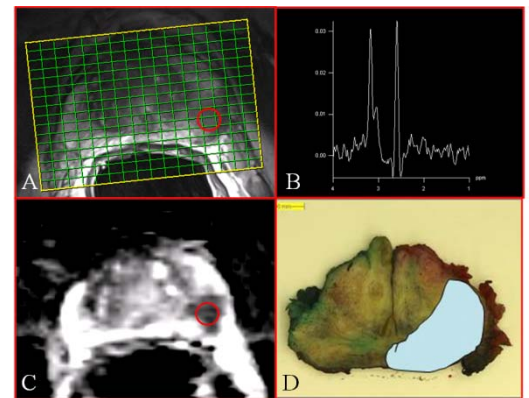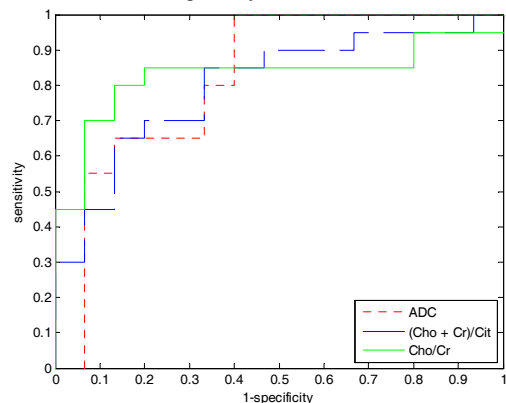

Figure 1. MRI (A) and DWI (C) of the prostate with a tumor in the peripheral zone, as shown on the histopathology (D). (B) shows the spectrum of a tumor-containing voxel surrounded by a sphere in (A) which is used for calculation of the local median ADC value in (C).

	AUC	Sensitivity	Specificity	PPV	NPV
ADC	0.82 (0.67-0.97)	0.65	0.87	0.87	0.65
(Cho + Cr)/Cit	0.80 (0.65-0.95)	0.70	0.80	0.82	0.67
Cho/Cr	0.83 (0.68-0.98)	0.80	0.87	0.89	0.76
LDA	NA	0.85	0.87	0.89	0.81

Table 1. The sensitivity, specificity, PPV and NPV calculated from the optimal cut-off of the ROC curve (Figure 2) and the AUC (with 95% confidence intervals) using only the ADC, (Cho + Cr)/Cit and Cho/Cr ratios, respectively, as variable. The performance of the LDA is also shown using all three measures as input for classification.

Figure 2. The ROC curves show the individual performance of ADC, (Cho+Cr)/Cit and Cho/Cr ratios to discriminate low- and high-grade tumors.

Discussion/Conclusion

In this study we validated that MRSI and DWI can help in the discrimination of high Gleason tumors from low Gleason tumors with histopathology as a gold standard. Moreover, combining the local minimum of the ADC values and the maximum metabolic ratios in the area labeled as tumor, applying LDA, resulted in a higher specificity and sensitivity for separating low- and high grade tumors than using one modality alone. This suggests that the two methods have complementary value in separating tumors into different classes. Future work in a prognostic setting based on the proposed combination of methods with the LDA needs to confirm this validation study and show if the multi-parametric approach has prognostic value in the non-invasive assessment of prostate cancer aggressiveness

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