Detection of prostate cancer: Utility of diffusion-weighted MR imaging and 3D MR spectroscopic imaging

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Abstract  Purpose: To prospectively compare the mean ADC generated from DWI, the mean choline + creatine/citrate ratio generated from 3D MRS and the combined mean ADC and mean choline + creatine/citrate ratio in the detection of prostate cancer, and to correlate between the choline + creatine/citrate ratio and the aggressiveness of malignancy determined by Gleason score, with histopathological examination of the excised gland as the reference standard.

Patients and methods: Forty-six patients with biopsy-proved cancer underwent pre-operative MRI at 1.5 T. Axial T1, axial, coronal and sagittal T2-weighted, diffusion-weighted and 3D MRS using a point-resolved spectroscopic sequence (PRESS) were acquired. The mean ADC, mean choline + creatine/citrate ratio and combined parameters for malignant lesions are correlated with the pathological results. For each malignant lesion choline + creatine/citrate ratio was correlated with the aggressiveness of malignancy determined by Gleason score. Receiver operating characteristic (ROC) curves were used to determine sensitivity, and specificity of the studied parameters, and Kappa measures of agreement were calculated for prostate cancer detection.

Results: The mean ADC for tumor tissue was 1.0 ± 0.22 × 10⁻³ mm²/s (mean ± SD), and was significantly lower than that for non-tumor tissue 1.44 ± 0.28 × 10⁻³ mm²/s (p < 0.001). For MRS study the mean (choline + creatine)/citrate ratio in tumor tissue was 1.98 ± 1.0, and was significantly higher than that for non-tumor tissue, 0.72 ± 0.39 (p < 0.001). By combining both ADC values and (choline + creatine)/citrate ratio for differentiating malignant from non-malignant...
1. Introduction

Despite the recent development in the diagnosis and the treatment of prostatic cancer, it continues to be the most common cancer and the third leading cause of death in men (1). The choice of treatment depends on a number of clinical parameters and clinical nomograms such as the patient’s age at diagnosis, the stage and the aggressiveness of the tumor (2), with the highest priority being the differentiation between indolent and aggressive disease, which is based mainly on Gleason grade determined by TRUS-guided biopsy (2). However, US is of low accuracy in detection and localization of prostate cancer, so a random instead of targeted biopsy is performed.

Random sampling has several disadvantages such as missing of the cancer located outside the routine biopsy site and unnecessary sampling of normal prostatic tissue. Moreover, the site of previously negative biopsy cannot be determined in patient with continuously high Prostatic Surface Antigen (PSA) and the biopsy is repeated (3). Thus a non-invasive technique that allows accurate detection and assessment of the degree of aggressiveness of prostatic cancer is needed to make a substantial contribution to the decision-making process for proper treatment selection (2).

The use of MRI as a non-invasive tool for the evaluation and management of prostatic cancer has grown steadily in the past decades (4). It allows functional assessment by different techniques such as diffusion-weighted images (DWI) and MR spectroscopy (MRS) (5). At 2WI prostate cancer appears as a focus of low-signal intensity relative to bright normal peripheral zone. However, prostate cancer is difficult to detect when it is in the central zone due to high-signal intensity from benign prostatic hypertrophy (6). The accuracy of T2-weighted MRI in tumor localization is 67–77% (7).

Diffusion-weighted MRI (DWI), a non-invasive technique in which molecular motion of water is measured in biological tissues, is now used in the detection of prostate cancer as an adjunct to T2WI (8). The apparent diffusion coefficient (ADC) calculated from DWI in prostate cancer showed that the mean ADC for malignant prostate is lower than the mean ADC in the non-malignant prostatic tissue (9–11).

MR spectroscopic imaging has shown to provide an incremental value to MRI regarding tumor detection and localization (12), by providing information on relative concentration of metabolites such as citrate (Cit), choline (Cho) and creatine (Cr) within a voxel (13).

In a previous study (14) a positive correlation between ADC values, metabolites ratio (Cit to Cho and Cr) and PSA was observed, and there was a direct relationship between the reduction in (Cit) level and the malignant changes in prostate (15).

Thus the purpose of this study is to evaluate the role of the mean ADC with DWMRI and the mean metabolic ratio with 

\[ \text{Cho + Cr)} \div \text{Cit} \]

MR spectroscopic imaging in the detection of prostatic cancer as well as the degree of aggressiveness of the lesion with post-operative histopathological examination as the reference standard.

2. Patients and methods

2.1. Patient characteristics

Forty-six men (mean age 61.5 ± 12.2 years) were included in this prospective study who were scheduled for radical retropubic prostatectomy or transurethral resection of the prostate due to biopsy-proved cancer, within a mean 23 ± 19 days. A minimum delay of 6 weeks was required between biopsy and MR imaging and MR spectroscopic imaging to minimize biopsy artifacts. Patient exclusion criteria were previous hormonal therapy, positive lymphadenectomy results, and contraindications to MR imaging (e.g., cardiac pacemakers, intracranial clips). Informed consent was obtained from all patients.

2.2. MR imaging protocol

MR imaging was performed with a 1.5-T Philips Achieva system by using a pelvic phased-array coil with the patient in supine position. MR imaging examination included conventional, DW imaging and MR spectroscopy imaging.

2.2.1. Conventional images

After localizer images, conventional images were obtained including transverse T1-weighted spin-echo MR images from the aortic bifurcation to the symphysis pubis with the following parameters: repetition time ms/echo time ms, 520/15 section thickness, 4 mm; intersection gap, 1 mm; field of view, 20 cm; matrix, 256 × 192 and flip angle 90 deg. Thin-section high-spatial-resolution transverse T2-weighted fast spin-echo MR images of the prostate and seminal vesicles were obtained with the following parameters: 3500/90, section thickness,
was performed by using only (Cho + Cr)/Cit and without reference to the MR imaging findings or knowledge of the results of pathologic evaluation.

2.3. Pathologic evaluation

Prostatectomy specimen was prepared and fixed in 10% formalin. After paraffin embedding, microslices were placed on glass slides and stained with hematoxylin and eosin. At pathologic analysis, grading was assigned to the lesion in the specimen according to the Gleason score.

2.4. Data and statistical analysis

Table 1 Regression model for combining ADC and (choline + creatine)/citrate ratio.

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*a</td>
<td>ADC</td>
<td>6.075</td>
<td>1.336</td>
<td>20.684</td>
<td>1</td>
<td>0.000</td>
<td>435.001</td>
<td>31.727</td>
</tr>
<tr>
<td></td>
<td>MRS</td>
<td>−1.864</td>
<td>0.554</td>
<td>11.312</td>
<td>1</td>
<td>0.001</td>
<td>0.155</td>
<td>0.052 0.459</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>−6.154</td>
<td>1.782</td>
<td>11.923</td>
<td>1</td>
<td>0.001</td>
<td>0.002</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*a Variable(s) entered on step 1: ADC, MRS.

Statistical analysis was performed by using statistical software SPSS version 10. (Cho + Cr)/Cit value for each suspicious voxel within the lesion was tabulated. The mean values of (Cho + Cr)/Cit for each lesion and the total number of suspicious voxels in the lesion were recorded for statistical analysis. We used the mean ADC and the mean (choline + creatine)/citrate ratio for each multivoxel ROI. The mean values of the benign ROIs were compared with the mean values of the malignant ROIs by using paired *t* tests.

Diffusion-weighted information and 3D MR spectroscopic imaging information were combined by using generalized estimating equations with an independent working correlation matrix to account for the correlated data. To obtain predicted probabilities of an ROI being cancerous, the mean ADC and the mean (choline + creatine)/citrate ratio for each ROI were entered into a logistic regression model. On the basis of the results of this model (Table 1), the following equation was obtained for the probability of an ROI being cancerous:

\[-6.15 + \text{ADC} \times 6.07 = \text{MRS} \times 1.864\]

The regression model yielded estimated regression coefficients that weighted the information from these two variables in an optimal way for combining them. The regression analysis also determined whether each variable was significantly associated with the probability of an ROI being cancerous, after adjusting for the other information. Receiver operating characteristic curves and the corresponding areas under the receiver operating characteristic curves (AUCs) were estimated non-parametrically for the detection of cancer by using mean ADC, mean (choline + creatine)/citrate ratio, and combined mean ADC and mean (choline + creatine)/citrate values for each ROI. In all statistical methods, a *p* value of less than 0.05 was considered to indicate a significant difference. Because smaller ADC values are associated with cancer, for the receiver operating characteristic analysis we transformed the ADC value by multiplying it by −1. The sensitivity and specificity of mean ADC, mean (choline + creatine)/citrate ratio,
and combined mean ADC and mean (choline + creatine)/citrate were measured and Kappa measures of agreement were calculated.

MR spectroscopic imaging sensitivity for cancer detection was analyzed prospectively by comparing the MR spectroscopic imaging voxels, which had been designated as suspicious for cancer, with the pathologic findings. Sensitivity was calculated for all pathologic lesions as a group and for individual Gleason score groups (3 + 3, 3 + 4, 4 + 3, and ≥4 + 4). Then MR spectroscopic imaging analysis tested the hypothesis that MR spectroscopic imaging metabolite ratios in true-positive lesions were related to pathologic Gleason scores. The relationship of Gleason scores for the individual lesions to the MR spectroscopic imaging (Cho + Cr)/Cit value was assessed. In each lesion, the MR spectroscopic imaging mean ratio was compared with the Gleason score for that lesion.

3. Results

A total of 46 patients underwent conventional MRI, DWI, and MRS for prostatectomy. Twelve patients had a single lesion, nineteen patients had two lesions, nine patients had three lesions and seven patients had four lesions.

There was an overlap between tumor and non-tumor mean ADC values and the mean (choline + creatine)/citrate ratio (Fig. 1A and B).

The mean ADC for tumor tissue was $1.0 \pm 0.22 \times 10^{-3}$ mm$^2$/s (mean ± SD), and was significantly lower than that for non-tumor tissue $1.44 \pm 0.28 \times 10^{-3}$ mm$^2$/s ($p < 0.001$) (Table 2).

All prostatic cancer displayed high-signal intensity on DWI and low-signal intensity on ADC map.

For MRS study the mean (choline + creatine)/citrate ratio in tumor tissue was $1.98 \pm 1.0$, and was significantly higher than that for non-tumor tissue $0.72 \pm 0.39$ ($p < 0.001$) (Table 2).

By combining both ADC values and (choline + creatine)/citrate ratio for differentiating malignant from non-malignant tissues a receiver operating characteristic analysis (ROC) curve showed Area under curve (AUC) = 0.93, 95% CI: 0.88–0.97 and was significantly higher than that (choline + creatine)/citrate ratio alone where AUC = 0.86, 95% CI: 0.80–0.92 ($p < 0.001$) or ADC value alone where AUC = 0.89, 95% CI: 0.83–0.95 ($p < 0.001$). The latter was more accurate than (choline + creatine)/citrate ratio alone, although the difference was not significant ($p > 0.05$) (Fig. 2).

Of 151 lesions that were present in 46 patients included in this study and were identified with pathologic examination, 105 lesions were detected by MRS. Of these 105 lesions detected by MRS, 56 lesions had a Gleason score 3 + 3, 26 lesions had a Gleason score of 3 + 4, 11 lesions had a Gleason score of 4 + 3 and 12 lesions had a Gleason score P4+4.

Table 4 shows the sensitivity of MRS for tumor detection as graded by Gleason score. A greater sensitivity 85% and 92% was present for tumors with Gleason score 4 + 3 and

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**Table 2** Mean ADC values (mean ± SD) and mean (choline + creatine)/citrate ratio in malignant and benign tissues.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean</th>
<th>t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC ($\times 10^{-3}$ mm$^2$/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>1.0 ± 0.22</td>
<td>10.1</td>
</tr>
<tr>
<td>Benign</td>
<td>1.44 ± 0.28</td>
<td>6.9</td>
</tr>
<tr>
<td>(Choline + creatine)/citrate ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>1.98 ± 1.0</td>
<td>6.9</td>
</tr>
<tr>
<td>Benign</td>
<td>0.72 ± 0.39</td>
<td>6.9</td>
</tr>
</tbody>
</table>

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**Fig. 1** Box plot: (A) the mean ADC, (B) the mean (choline + creatine)/citrate ratio in malignant and benign tissues.

**Fig. 2** ROC curve shows mean ADC alone (green line) (AUC = 0.89), (choline + creatine)/citrate ratio alone (red line) (AUC = 0.86), and both ADC and (choline + creatine)/citrate ratio (blue line) (AUC = 0.93).
For the discrimination between Gleason score in tumors according to mean (choline + creatine)/citrate ratio there was a significant difference in lesions with low Gleason score (3 + 3) versus lesions with higher Gleason score (4 + 3 or 4 + 4) (<p value < 0.001), while lesions with Gleason score (4 + 3) did not differ significantly from those with Gleason score ≥4 + 4 (p > 0.05) (Table 5). Representative cases are shown in Figs. 4–8.

4. Discussion

Recent advances offer newly developed sequences for MR imaging. DWI has recently received attention as a promising method in the diagnosis of prostate cancer. Currently, it is the only technique that depicts differences in molecular diffusion. Restricted diffusion in tumor tissue is attributed to histopathological characteristics, such as greater cellular density caused by a high index of neoplastic replication, enlargement of nuclei and hyperchromatosis (16–19). The changes in diffusion properties are calculated by the apparent diffusion coefficient (ADC) which is affected by both the Brownian motion of water molecules and polluting factors from T2 tissue signals (20). So cellular changes that inhibit the movement of water molecules result in restricted diffusion and decreased ADC values in tumor tissues (21).

Several studies (22–24) have reported the high performance of DWI in detecting prostate cancer. In agreement with previous studies (9,25–30) this study showed that the ADC value for malignant tissue was significantly lower (<p value < 0.001) than that for non-malignant tissue. It was 1.0 ± 0.22 for tumor tissue and 1.44 ± 0.28 for non-tumor tissue. The sensitivity specificity for detecting prostate cancer were 81% and 84%, respectively. However, other studies (15,25,31) showed that the mean ADC values fall within a wide range of values for tumor and non-tumor tissue. They explained the wide variation in ADC values by physiologic factors such as age, tumor size and grade and by technical factors such as variations in acquisition parameters and post-processing techniques.

MRS provides an idea about the relative concentration of chemical metabolites in the prostatic tissue by using a small values of interest (voxels) (1,2).

3D MRS detects the level of metabolites such as citrate, choline and creatine, and making it possible to differentiate tumor from non-tumor tissue. In prostate cancer the reduced

### Table 3
Area under curve (AUC), sensitivity and specificity of studied parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (PPV)</th>
<th>Negative predictive value (NPP)</th>
<th>Kappa test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>0.89</td>
<td>81</td>
<td>84</td>
<td>92.4</td>
<td>66.1</td>
<td>0.60</td>
</tr>
<tr>
<td>(Cho + Cr)/Cit ratio</td>
<td>0.86</td>
<td>71.4</td>
<td>78.3</td>
<td>88.2</td>
<td>54.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Combined ADC and (Cho + Cr)/Cit ratio</td>
<td>0.93</td>
<td>94.2</td>
<td>85</td>
<td>93</td>
<td>86</td>
<td>0.80</td>
</tr>
</tbody>
</table>

### Table 4
Sensitivity of (choline + creatine)/citrate ratio for detection of pathologically proved tumor as graded by Gleason score.

<table>
<thead>
<tr>
<th>(Cho + Cr)/Cit ratio</th>
<th>Gleason score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 + 3</td>
</tr>
<tr>
<td>True positive</td>
<td>56</td>
</tr>
<tr>
<td>False negative</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>63</td>
</tr>
</tbody>
</table>

![Error bar showing mean (choline + creatine)/citrate ratio versus Gleason score. *NB: there is an increasing (choline + creatine)/citrate ratio with increasing Gleason score.](image)

For the discrimination between Gleason score in tumors according to mean (choline + creatine)/citrate ratio there was a significant difference in lesions with low Gleason score (3 + 3) versus lesions with higher Gleason score (4 + 3 or ≥4 + 4) (<p value < 0.001), while lesions with Gleason score (4 + 3) did not differ significantly from those with Gleason score ≥4 + 4.
Prostate cancer with Gleason score 4 + 4: axial T2WI (a) shows the cancer as an ill-defined hypointense focal lesion at central prostatic zone mainly to the left side. The tumor is hyperintense at DWI (b) and is of low-signal intensity at ADC map (c). 3D MRS at the same level (d), 3D MRS of a voxel at the cancer site (e) shows elevated Cho + Cr/Cit ratio and 3D MRS of a voxel at a normal site (f) shows normal Cho + Cr/Cit ratio.
Fig. 5  Prostate cancer with Gleason score $3 + 4$: axial $T_2$WI (a) shows the cancer as a small well-defined hypointense focal lesion at the left prostatic lobe. The tumor is hyperintense at DWI (b) and is of low-signal intensity at ADC map (c). 3D MRS of the same section (d), 3D MRS of a cancerous voxel (e) shows elevated Cho + Cr:Cit ratio and 3D MRS of a normal voxel (f) shows normal Cho + Cr:Cit ratio. A photomicrograph (g) shows Gleason score $3 + 4$. 
citrate level is due to conversion from citrate-producing to citrate-oxidizing metabolism, also the elevated choline level is due to increased cell growth and proliferation of tumor cells as its related phospholipid cell membrane turnover (1,2).

The choline and creatine are used in the spectral analysis in 3D MRS because both peaks are close to each other in the spectral trace and even may be inseparable (2).

In this study we used 3D MRS to evaluate prostatic tissue. By applying \((\text{Cho} + \text{Cr})/\text{Cit}\) ratio, this study showed that it was possible to differentiate tumor tissue by high \((\text{Cho} + \text{Cr})/\text{Cit}\) ratio \((1.98 \pm 1.0)\) for non-tumor tissue with significantly lower ratio \((0.72 \pm 0.39)\) \((p < 0.001)\). The sensitivity and specificity for 3D MRS in this study were 71.4\% and 78.3\%, respectively. These findings agreed with the previous studies (7,32–37) regarding the ability of MRS to differentiate tumor from non-tumor tissue.

The strategy of cancer care in the new millennium is directed toward maximizing cancer control while minimizing the risk of complication. The treatment of prostate cancer varied from deferred therapy (watchful waiting), hormonal ablation, radical surgery and different types of radiation therapy (38). The variability in biological aggressiveness, and the biopsy specimen are not accurate predictor of Gleason score and are the most challenging characteristics of prostate cancer (2).

Regarding the degree of aggressiveness of prostate cancer, this study showed that there was a trend toward an increasing \((\text{Cho} + \text{Cr})/\text{Cit}\) ratio in association with higher Gleason score. MRS showed higher sensitivity in detecting tumors of higher degree of aggressiveness and was 92\% in Gleason score \(\geq 4 + 4\), and 85\% in Gleason score \(4 + 3\); however, the sensitivity was 63\% for Gleason score \(3 + 3\). There were a significant difference \((p < 0.001)\) in discriminating between lesions.

Fig. 6  Prostate cancer with Gleason score 4 + 5: axial (a) and sagittal (d) T2WI show multiple cancerous well-defined hypointense focal lesions. The lesions are of high-signal intensity at DWI (b) and of low-signal intensity at ADC map (c). 3D MRS of the same section (e) and 3D MRS of a cancerous voxel (f) shows elevated Cho + Cr/Cit ratio. A photomicrograph (g) shows Gleason score 4 + 5.
with low Gleason score 3 + 3 and those with higher Gleason score (4 + 3 or ≥4 + 4). These findings agreed with the previous studies (39,40) regarding the correlation between MRS (metabolite ratio) and tumor grade.

Previous studies (7,14,28) suggested that the combination of both ADC and MRS has improved the diagnostic accuracy. In consistence with these findings, our study showed that the combination of both ADC and MRS had a higher sensitivity 94.2% and specificity 85% than each parameter alone. The AUC in the combined parameters was 0.93 (Kappa test = 0.80) which is significantly higher ($p < 0.001$) than ADC alone where AUC = 0.89 and Kappa test 0.60 or (Cho + Cr)/Cit ratio alone (AUC = 0.86 and Kappa test = 0.44). However, Mazaheri et al. (15) stated that combined DWI and MRS was not significantly more accurate than DWI alone.

In conclusion, the diagnostic power of combined DWI and MRS in discrimination between tumor and non-tumor tissue in prostate cancer is higher than a single parameter. The ability of MRS to predict and discriminate between different degrees

**Fig. 7** Prostate cancer with Gleason score 4 + 3: axial T2WI (a) shows the cancer as an ill-defined hypointense focal lesion at the right prostatic lobe. The tumor is hyperintense at DWI (b) and is of low-signal intensity at ADC map (c). MRS of the cancerous voxel (d) shows elevated Cho + Cr/Cit ratio. Photomicrographs (e and f) show Gleason score 4 + 3.
of aggressiveness of prostate cancer as graded by Gleason score would warrant the use of MRS in conjunction with DWI as a promising non-invasive parameters for the diagnostic workup of prostate cancer.

Fig. 8 Prostate cancer with Gleason score 4 + 3: axial T2WI (a) shows the cancer as an ill-defined iso- to hypointense focal lesion at central prostatic zone. The tumor is hyperintense at DWI (b) and is of low-signal intensity at ADC map (c). 3D MRS at the same level (d), 3D MRS of a voxel at the cancer site (e) shows elevated Cho + Cr/Cit ratio, and 3D MRS of a voxel at a normal site (f) shows normal Cho + Cr/Cit ratio.
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