Role of Endorectal Magnetic Resonance Spectroscopic Imaging in Two Different Gleason Scores in Prostate Cancer

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Key Words

Magnetic resonance spectroscopic imaging • Prostate cancer • Choline groups • Citrate • Creatine

Abstract

Objective: The major goal of the work was to record three-dimensional magnetic resonance spectroscopic imaging (MRSI) and to compare metabolite ratios between different Gleason scores (GS). **Materials and Methods:** MRSI localized by endorectal coil-acquired point-resolved spectroscopy was performed in 14 men with prostate cancer of GS 6 (n = 7) and 7 (n = 7) using a 1.5-tesla MRI scanner. **Results:** The ratio of (choline + creatine)/citrate was increased with an increase of GS, i.e. 0.590 ± 0.171 in the target lesion and 0.321 ± 0.157 in the contralateral region of patients with a GS of 6 as opposed to 1.082 ± 0.432 in the target lesion and 0.360 ± 0.243 in the contralateral region of patients with a GS of 7. **Conclusion:** Our pilot results demonstrated that MRSI was an additional biochemical tool which is complementary to the current imaging modalities for early diagnosis and therapeutic management of prostate cancer.

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Introduction

Prostate cancer is the most common noncutaneous malignancy and the second leading cause of death from cancer, after lung cancer, in American men [1]. As with any cancer, if it is advanced or left untreated in early stages, it can eventually spread through the blood and lymph network to other organs. Fortunately, prostate cancer tends to be slow-growing compared to other cancers. The term 'grade' describes how closely the tumor resembles normal prostate tissue. The most widespread way of grading prostate cancer is called the Gleason system and this system uses a Gleason score (GS) of 2–10 to grade prostate cancer, where higher grades represent more aggressive tumors [2–4]. The GS offers a good clue of the tumor's behavior as the prostate tumor with a low GS is likely to be slow-growing, while one with a high score is more likely to grow aggressively or to have already spread outside the prostate (metastasized).

Magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) enable anatomic and metabolic evaluation of the prostate gland. The MRSI is a powerful technique for local evaluation of prostate cancer growth and aggressiveness. MRSI facilitates the demonstration of normal and altered tissue metabolism,

and is therefore different from other imaging methods that only assess abnormalities of structure. The primary MRSI technique that is currently available commercially utilizes the point-resolved spectroscopy sequence [5], with spectral spatial pulses for lipid suppression [6–8]. In particular, endorectal MRI and MRSI have shown considerable promise in the evaluation of tumor extent and aggressiveness in patients with biopsy-proven prostate cancer [9–11] and might be valuable in tumor diagnosis.

Cancer tissue can appear in any place in the prostate, and so the use of a three-dimensional (3D) MRSI method to cover the whole prostate is necessary [12]. MRI may improve the staging of prostate cancer compared with clinical evaluation alone, computer tomography, or transrectal ultrasound, as it allows simultaneous and detailed assessment of prostatic, periprostatic, and pelvic anatomy. Earlier reports suggesting a limited applicability of MRI did not incorporate MRSI or the use of endorectal coils, and they used sequences and equipment that were not up to current standards. The value of MRSI to detect and localize cancer in the transition zone of the prostate has been reported [13, 14]. Prostate cancer has been shown to be characterized by a decreased signal of citrate (Cit) and an increased signal of choline (Cho)-containing compounds. Therefore, a commonly used marker for cancer tissue is the ratio of [Cho + creatine (Cr)]/Cit. The purpose of the study was to record 3D MRSI and to compare metabolite ratios using spectroscopic imaging data between 2 different Gleason scores ($3 + 3 = 6$ vs. $4 + 3 = 7$).

Materials and Methods

The entire protocol was approved by the Institutional Review Board, and informed consent was obtained from each patient. Patient selection was limited to GS 6 or 7 and prostatectomy. Fourteen men [$n = 7$ with a GS ($3 + 3$) and $n = 7$ with a GS ($4 + 3$)] underwent radical retropubic prostatectomy, and their pathologies were subsequently analyzed. These patients were scanned using a 1.5-tesla Siemens (Siemens Medical Solution, Erlangen, Germany) MRI scanner with an endorectal coil. The protocol combining MRI and MRS was performed at least 8 weeks after transrectal ultrasound-guided sextant biopsy. MRI included T_2 -weighted images acquired with a fast spin-echo sequence with: repetition time (TR) = 3,800 ms, effective echo time (TE) = 101 ms, slice thickness = 3 mm, field of view = 140 mm, and matrix size = 256×256 . The ages of the patients ranged from 52 to 78 years, and the patients had 2 different GS: $3 + 3$ (mean $\pm$ SD, 56.8 ± 7.9 years) and $4 + 3$ (mean $\pm$ SD, 64.8 ± 8.6 years). The mean and standard deviation of prostate-specific antigen value for the patients with a GS of $3 + 3$ was 7.2 ± 2.5 ng/ml. For patients with a GS of $4 + 3$, it was 13.5 ± 3.1 ng/ml.

MRSI was performed in all patients, including water- and fat-suppressed acquisition. The parameters were: TR/TE/Avg/BW = 700 ms/120 ms/6 ms/1,300 Hz, and 512 spectral data points, where TR, TE, Avg, and BW represent repetition time, echo time, averages and spectral bandwidth. The field of view was $80 \times 80 \times 80$ mm³ with a raw matrix size of $512 \times 12 \times 12$. A point-resolved spectroscopy pulse sequence was used to acquire the proton MR spectra from a volume of interest of $55 \times 40 \times 40$ mm³. Outer volume lipid suppression was achieved using eight 3-cm slab saturation pulses around the volume of interest. Water and fat resonances were suppressed using two 12.6-ms dual-frequency selective MEGA pulses [15] with crusher gradients. A TE of 120 ms was used for optimal Cit detection.

The spectroscopy software on the MR scanner provided by the manufacturer was used to evaluate the (Cho + Cr)/Cit ratio. For 3D MRSI postprocessing, each spectrum was Fourier transformed, frequency-, phase-, and baseline-corrected, and peaks of Cit, Cho and Cr were subsequently fitted. Hamming filter was used for the MRSI spatial dimensions of the data. For the statistical analysis, the Student *t* test was used to compare the ratios between different GS, and a *p* value of less than 0.05 was considered to indicate a significant difference. A radiologist (D.M.) and a physicist (M.A.T.), both with more than 10 years of experience in analyzing prostate endorectal MRI and MRSI data, interpreted the imaging studies using established morphologic and metabolic criteria for the MRI and MRSI evaluation of prostate cancer. The spectroscopist evaluated the MRSI data set and provided the location and number of suspicious voxels to the radiologist, who integrated the MRSI information with the MRI data and provided a final reading for each study. In the decision status for classifying voxels as noncancerous or malignant, the voxels were first broken up according to their GS and noncancerous regions. If the Cit peak was lower than the Cho peak or was undetectable, the voxel was determined to be malignant. If the Cit peak was higher than the Cho peak, the voxel was considered noncancerous for (Cho + Cr)/Cit smaller than 0.37 and malignant for (Cho + Cr)/Cit greater than 0.37.

Statistical Test

The mean and standard deviation of (Cho + Cr)/Cit were calculated. Statistical analysis was conducted using the Student *t* test between 2 different GS. A value of $p < 0.05$ was considered to be significant.

Results

The one-dimensional (1D) spectra extracted from the 3D MRSI data recorded in the affected and contralateral area of a 67-year-old prostate cancer patient with a GS of 6 ($3 + 3$) are shown in figure 1a and b, and the corresponding voxel locations are presented in figure 1c and d. Similarly, the 1D spectra extracted from the 3D MRSI data recorded in the affected and contralateral area of a 70-year-old prostate cancer patient with a GS of 7 ($4 + 3$) are shown in figure 2a and b. In prostate cancer patients with a GS of $3 + 3$, the (Cho + Cr)/Cit ratios in the affected side were

Fig. 1. Spectroscopic imaging of a 67-year-old prostate cancer patient with a GS 3 + 3. **a, b** The 1D spectra extracted from the 3D MRSI data recorded in the affected and contralateral area. **c, d** The corresponding voxel locations.

Table 1. Metabolite (Cho + Cr)/Cit ratios calculated using the 3D MRSI data recorded in 2 different grades

Location	Contralateral regions	Lesion with GS 3 + 3 (n = 7)
GS of 6 (i.e. 3 + 3)		
Apex	0.208 ± 0.074	0.522 ± 0.066
Midgland	0.192 ± 0.157	0.377 ± 0.328
Base	0.321 ± 0.157	0.590 ± 0.171
Location	Contralateral regions	Lesion with GS 4 + 3 (n = 7)
GS of 7 (i.e. 4 + 3)		
Apex	0.303 ± 0.025	0.580 ± 0.134
Midgland	0.198 ± 0.142	0.442 ± 0.174
Base	0.360 ± 0.243	1.082 ± 0.432

0.522 ± 0.066 , 0.377 ± 0.328 and 0.590 ± 0.171 in the apex, midgland and base regions, respectively. In contrast, these ratios in the apex, midgland and base regions of the contralateral side were 0.208 ± 0.074 , 0.192 ± 0.157 and 0.321 ± 0.157 , respectively. On the other hand, these ratios in prostate cancer patients with a GS of 4 + 3 were as follows: 0.580 ± 0.134 , 0.442 ± 0.174 and 1.082 ± 0.432 in the apex, midgland and base regions of the affected side and 0.303 ± 0.025 , 0.198 ± 0.142 and 0.360 ± 0.243 in the contralateral side, as summarized in table 1. There were no statistically significant changes observed in the (Cho + Cr)/Cit ratios with GS. However, a trend was visible, i.e. GS 7 had a higher (Cho + Cr)/Cit ratio compared to GS 6.

Discussion

Endorectal MRI and MRSI facilitate improved diagnosis of prostate cancer in patients with 2 different GS. The ratio of (Cho + Cr)/Cit is capable of distinguishing between healthy and cancerous prostate tissues. MR

Fig. 2. Spectroscopic imaging of a 70-year-old prostate cancer patient with a GS 4 + 3. **a, b** The 1D spectra extracted from the 3D MRSI data recorded in the affected and contralateral area. **c, d** The corresponding voxel locations.

spectroscopy of the prostate is a noninvasive approach for the detection of prostate cancer, and the potential of MR spectroscopy to identify intraprostatic cancer foci in addition to MRI with a high sensitivity and specificity has already been proven in several studies [16, 17]. So far, the emphasis in MRSI of the prostate was placed on the peripheral zone [18] resulting from the fact that the signal-to-noise ratio in the peripheral zone is superior to the central gland because the endorectal coil is positioned against the dorsal part of the prostate which contains the peripheral zone. Seventy percent of tumor nodules are present in the peripheral zone [19, 20]. As the GS increased, the metabolite ratio of (Cho + Cr)/Cit also elevated. Numerous investigators have also found elevated Cho levels in tumors [21–23]. Since these compounds are anabolites (Cho and phosphocholine) and catabolites (glycerophosphocholine) of phosphatidylcholine, which is a major membrane phospholipid, it has been suggested that the elevated Cho level reflects an elevated cell proliferation rate, and there are some data to support this hypothesis [24]. Even though the metabolite ratio measured

by MRSI did not show statistically significant changes, there are higher levels of Cho-containing metabolites in prostate cancers having higher Gleason grades, which agrees with a previous study [25]. There is an overlap between MRSI parameters at various GS levels, which may reflect methodological and physiological variations.

Conclusion

Our study showed that the metabolite ratio of (Cho + Cr)/Cit in MRSI measurement of prostate cancer increased with an increase of these 2 GS (GS 3 + 3 and GS 4 + 3). MRSI has potential in noninvasive evaluation of prostate cancer aggressiveness.

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References

- 1 Jemal A, Thun MJ, Ries LA, Howe HL, Weir HK, Center MM, Ward E, Wu XC, Ehemann C, Anderson R, Ajani UA, Kohler B, Edwards BK: Annual report to the nation on the status of cancer, 1975–2005, featuring trends in lung cancer, tobacco use, and tobacco control. *J Natl Cancer Inst* 2008;100:1672–1694.
- 2 Kattan MW, Eastham JA, Stapleton AMF, Wheeler TM, Scardino PT: A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst* 1998;90:766–771.
- 3 Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J: Long-term survival among men with conservatively treated localized prostate cancer. *JAMA* 1995;274:626–631.
- 4 Gleason DF: Classification of prostatic carcinomas. *Cancer Chemother Rep* 1966;50:125–128.
- 5 Bottomley PA: Spatial localization in NMR spectroscopy in vivo. *Ann NY Acad Sci* 1987;508:333–348.
- 6 Brown TR, Kincaid BM, Ugurbil K: NMR chemical shift imaging in three dimensions. *Proc Natl Acad Sci USA* 1982;79:3523–3526.
- 7 Star-Lack J, Nelson SJ, Kurhanewicz J, Huang LR, Vigneron DB: Improved water and lipid suppression for 3D PRESS CSI using RF band selective inversion with gradient dephasing (BASING). *Magn Reson Med* 1997;38:311–321.
- 8 Schrickler AA, Pauly JM, Kurhanewicz J, Swanson MG, Vigneron DB: Dual-band spectral-spatial RF pulses for prostate MR spectroscopic imaging. *Magn Reson Med* 2001;46:1079–1087.
- 9 Bostwick DG, Graham SD Jr, Napalkov P, Abrahamsson PA, di Sant'agnese PA, Algaba F, Hoisaeter PA, Lee F, Littrup P, Mostofi FK: Staging of early prostate cancer: a proposed tumor volume-based prognostic index. *Urology* 1993;41:403–411.
- 10 Coakley FV, Kurhanewicz J, Lu Y, Jones KD, Swanson MG, Chang SD, Carroll PR, Hricak H: Prostate cancer tumor volume: measurement by endorectal MR imaging and MR spectroscopic imaging. *Radiology* 2002;223:91–97.
- 11 Scheidler J, Hricak H, Vigneron DB, Yu KK, Sokolov DL, Huang LR, Zaloudek CJ, Nelson SJ, Carroll PR, Kurhanewicz J: Prostate cancer: localization with three-dimensional proton MR spectroscopic imaging – clinico-pathologic study. *Radiology* 1999;213:473–480.
- 12 Scheenen TW, Klomp DW, Röhl SA, Fütterer JJ, Barentsz JO, Heerschap A: Fast acquisition-weighted three-dimensional proton MR spectroscopic imaging of the human prostate. *Magn Reson Med* 2004;52:80–88.
- 13 Zakian KL, Eberhardt S, Hricak H, Shukla-Dave A, Kleinman S, Muruganandham M, Sircar K, Kattan MW, Reuter VE, Scardino PT, Koutcher JA: Transition zone prostate cancer: metabolic characteristics at 1H MR spectroscopic imaging – initial results. *Radiology* 2003;229:241–247.
- 14 Akin O, Sala E, Moskowitz CS, Kuroiwa K, Ishill NM, Pucar D, Scardino PT, Hricak H: Transition zone prostate cancers: features, detection, localization, and staging at endorectal MR imaging. *Radiology* 2006;239:784–792.
- 15 Mescher M, Tannus A, Johnson MO, Garwood M: Solvent suppression using selective echo dephasing. *J Magn Reson A* 1996;123:226–229.
- 16 Kurhanewicz J, Vigneron DB, Hricak H, Narayan P, Carroll P, Nelson SJ: Three-dimensional H-1 MR spectroscopic imaging of the in situ human prostate with high (0.24–0.7 cm³) spatial resolution. *Radiology* 1996;198:795–805.
- 17 Hasumi M, Suzuki K, Taketomi A, Matsui H, Yamamoto T, Ito K, Kurokawa K, Aoki J, Endo K, Yamanaka H: The combination of multi-voxel MR spectroscopy with MR imaging improve the diagnostic accuracy for localization of prostate cancer. *Anticancer Res* 2003;23:4223–4227.
- 18 Zakian KL, Sircar K, Hricak H, Chen HN, Shukla-Dave A, Eberhardt S, Muruganandham M, Eboral L, Kattan MW, Reuter VE, Scardino PT, Koutcher JA: Correlation of proton MR spectroscopic imaging with Gleason score based on step-section pathologic analysis after radical prostatectomy. *Radiology* 2005;234:804–814.
- 19 Chen ME, Johnston DA, Tang K, Babaian RJ, Troncoso P: Detailed mapping of prostate carcinoma foci: biopsy strategy implications. *Cancer* 2000;89:1800–1809.
- 20 McNeal JE, Redwine EA, Freiha FS, Stamey TA: Zonal distribution of prostatic adenocarcinoma: correlation with histologic pattern and distribution of spread. *Am J Surg Pathol* 1988;12:804–814.
- 21 Heesters MA, Kamman RL, Mooyaart EL, Go KG: Localized proton spectroscopy of inoperable brain gliomas: response to radiation therapy. *J Neurooncol* 1993;17:27–35.
- 22 Sijens PE, Knopp MV, Brunetti A, Wicklow K, Alfano B, Bachert P, Sanders JA, Stillman AE, Kett H, Sauter R: 1H MR spectroscopy in patients with metastatic brain tumors: a multicenter study. *Magn Reson Med* 1995;33:818–826.
- 23 Rutter A, Hugenholtz H, Saunders JK, Smith ICP: One-dimensional phosphorus-31 chemical shift imaging of human brain tumors. *Invest Radiol* 1995;30:359–366.
- 24 Smith TA, Eccles S, Ormerod MG, Tombs AJ, Titley JC, Leach MO: The phosphocholine and glycerophosphocholine content of an oestrogen-sensitive rat mammary tumour correlates strongly with growth rate. *Br J Cancer* 1991;64:821–826.
- 25 Swanson MG, Vigneron DB, Tabatabai ZL, Males RG, Schmitt L, Carroll PR, James JK, Hurd RE, Kurhanewicz J: Proton HR-MAS spectroscopy and quantitative pathologic analysis of MRI/3D-MRSI-targeted post-surgical prostate tissues. *Magn Reson Med* 2003;50:944–954.