Clinical Efficacy of Proton Magnetic Resonance Spectroscopy (1H-MRS) in the Diagnosis of Localized Prostate Cancer

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Abstract. Background: The objective of this study was to evaluate the efficacy of proton magnetic resonance spectroscopy (1H-MRS) in the detection of prostate cancer. Materials and Methods: The experimental group consisted of 20 patients with localized prostate cancer who underwent radical prostatectomy. The sensitivity, positive predictive value and accuracy of the detection of prostate cancer in the 12 sections of the peripheral zone were calculated for prostate biopsy alone, 1H-MRS alone and the combination of these methods, respectively. Results: The sensitivity, the positive predictive value, and the accuracy of the preoperative diagnosis of prostate cancer were 43.7%, 68.9% and 54.6%, respectively, with prostate biopsy alone; 60.6%, 87.8% and 71.4% with 1H-MRS alone; and 88.7%, 88.7% and 87.4% with the combination of biopsy and 1H-MRS, respectively. Combined use of biopsy and 1H-MRS significantly improved the sensitivity, positive predictive value and accuracy of the diagnosis. Conclusion: 1H-MRS together with biopsy might improve the diagnostic accuracy in prostate cancer.

The incidence of prostate cancer was traditionally lower in Japan than in Western countries, although the mortality rate of prostate cancer is increasing in Japan, paralleling the increased performance of the PSA (prostate-specific antigen) test (1). Multi regional needle biopsy of the prostate has been the gold standard for achieving a definitive diagnosis of prostate cancer, but it has the drawback of often yielding false-negative results. The false-negative rate could be reduced in number by increasing the number of biopsy sites within the gland such as saturation biopsies (1), but that leads to a proportional increase in complications for the patient (2). In addition, prostate cancer is often multi focal within the gland and comparison with the histopathological findings after total prostatectomy shows that in many cases the biopsied sites represent only a portion of the entire malignancy (3). Accordingly, a method that is less invasive yet has better diagnostic power for prostate cancer is sorely needed. However, although progress has been made with such techniques as transrectal ultrasound (TRUS) (4), computed tomography (CT), magnetic resonance imaging (MRI) (5), and positron emission computed tomography (PET) (3), the results of these modalities remain unsatisfactory. The conventional body coil MRI has a moderate power for the diagnosis of prostate cancer. However, it showed low accuracy in identifying the distribution of malignant tissue within the prostate (4). The diagnostic power of endorectal coil MRI was investigated for localized prostate cancer that was confirmed by total prostatectomy, and it was reported that the accuracy was 61-90%, the sensitivity 50-100%, the specificity 36-83%, the positive predictive value 53-93% and the negative predictive value was 50-100% (6-10), however these values vary widely.

Normal prostate epithelial cells contain a high concentration of zinc. Zinc inhibits aconitase activity, thereby inhibiting the intracellular citric acid cycle. As a result, citric acid is not consumed, accumulates in the cells and is secreted into the glandular cavity (11). In contrast, in cancer cells, citric acid metabolism via the citric acid cycle is activated, and the citrate in the cells decreases. In addition, in cancer cells, there is an increase in choline containing substances, which cause vigorous cell membrane synthesis and breakdown (12).

MR spectroscopy is considered one of the most promising areas of prostate imaging research (13). Voxels, color-encoded to reflect abnormal ratios of metabolites, can be viewed directly as tumor maps (14). In the case of the normal prostate, 1H-
MRS shows a high peak for citrate and a low peak for choline containing substances. Conversely, for prostate cancer cells, \(^1\)H-MRS shows a low peak for citrate and a high peak for choline containing substances (Figure 1). On the basis of these characteristics, it can be surmised that the ratio of the peaks for citrate and choline containing substances can serve as a good index of prostate cancer. Accordingly, \(^1\)H-MRS is a diagnostic modality that is based on \textit{in vivo} metabolic information. Therefore, MR spectroscopy has been shown to improve detection of prostate cancer (15, 16).

For the present study, we performed \(^1\)H-MRS and needle biopsy of the prostate gland and investigated whether the combination of these two techniques has the potential to improve the accuracy of diagnosis of localized prostate cancer compared with each of these modalities alone.

**Patients and Methods**

\textit{Patients.} This study was carried out on 20 patients (median age: 67.0 years old, range: 51-77 years) who were diagnosed with T1c-T2, N0M0 localized prostate cancer by biopsy during the period from April 2003 to April 2006 and underwent radical prostatectomy.

\textit{Specimens of multi regional biopsy and radical prostatectomy.} The multi-regional prostate biopsies were performed under TRUS guidance, including 12 sections of the peripheral zone of the gland, as shown in Figure 2. The total prostatectomy specimens were handled in accordance with the Japanese guideline for prostate specimens (17) and were sliced into 5-mm-thick horizontal sections perpendicular to the dorsal surface of the urethral mucosa. The sections were fixed in formalin and stained with hematoxylin-eosin. The pathological diagnoses were performed by a single pathologist (Terado Y).

\(^1\)H-MRS. \(^1\)H-MRS was performed using a 1.5 Tesla MRI system (Signa LX Horizon Echospeed, General Electric Medical Systems, Inc., USA). The sequence and imaging conditions that were employed were as follows: Sequence = PRESS based 3DPROSE; TR/TE = 2000/130 msec; spectral width = 1250 Hz; data acquisition points = 256; activation area = 8.0 or 16.0 cm\(^2\); encode = 8\times8 or 16\times16; number of excitation = 2. A body coil was used as the transmission coil, while the receiver coil was an endorectal coil (BPX-10, Nihon Medrad K.K., Tokyo, Japan) placed on the anterior surface of the rectum in close contact with the posterior aspect of the prostate (18, 19). Spectral data correcting volume (VOI) was set on the axial localization image manually to cover the whole outer gland. The thickness of the VOI was 2.0 cm. Six planes of fat saturation pulse were set at a region adjacent to a VOI. Full width half maximum of water peak after shimming was less than 14 ppm in all subjects.

The processing of the \(^1\)H-MRS data was performed with the supplied processing software (SAGE II, General Electric Medical Systems, Milwaukee, USA) on the MRI console. Each spectral signal was zero filled to 512 points and multiplied by a 2 Hz of exponential function. Fourier transformation, phase adjustment, frequency adjustment, baseline correction and calculation of the CCr ratio were automatically performed. The median interval from the biopsy to performance of \(^1\)H-MRS was 80 days, and the median interval between \(^1\)H-MRS and total prostatectomy was 7.5 days.

**Results**

\textit{Cut-off value for CCR [(choline + creatine)/citrate] ratio in prostate cancer.} The slices of the total prostatectomy specimens were compared with the \(^1\)H-MRS images at the
corresponding level. The regions of interest (ROI) for the prostate cancer lesions and the normal prostate sites were decided and the CCr ratio was calculated (Figure 3a, b). Data were obtained from 51 loci of 10 patients, and the CCr ratios between the prostate cancer lesions and the normal peripheral zone were compared (Figure 4). The mean CCr ratio for the prostate cancer lesions was 1.40±0.20, compared with 0.75±0.16 for the normal prostate sites. On the basis of these data, it was decided that the cut off value for diagnosis of prostate cancer by $^1$H-MRS would be ≥1.07, which is equivalent to the mean +2 SD of the CCr ratio for cancerous prostate tissue.

Sensitivity, positive predictive value and accuracy in cases of diagnosis by biopsy, $^1$H-MRS and their combination. The cut-off value decided above was employed to retrospectively determine the location of lesions in the prostates of the remaining 10 patients by $^1$H-MRS. Next, the entire peripheral zone was divided into 12 sections (total n=120 sections). For each of the sections, the sensitivity and positive predictive values are shown for biopsy alone, $^1$H-MRS alone and biopsy with $^1$H-MRS combined. *p<0.001. White bar: prostate biopsy; shaded bar: MRS; black bar: prostate biopsy + MRS.
zone was divided into 12 sections according to the regions of biopsies as shown in Figure 2. Each of these regions was examined for the presence/absence of malignancy on the basis of biopsy and $^1$H-MRS alone as well as the combination of biopsy and $^1$H-MRS. In addition, the generated results were compared with the histopathological findings for the total prostatectomy specimens and the sensitivity, positive predictive value and accuracy were compared among the three diagnostic approaches of biopsy and $^1$H-MRS alone and in combination. In previous reports, the efficacy of MRS in the diagnosis of Transition zone carcinoma of the prostate gland was controversial, hence this investigation was limited to the peripheral zone (20).

Comparison of the distribution of peripheral zone sites showing a CCr ratio $\geq$1.07 on the $^1$H-MRS images with the corresponding slices of the total prostatectomy specimen showed that there was good agreement between the sites diagnosed as malignant by $^1$H-MRS and the sites of cancer loci upon histopathological inspection of the total prostatectomy specimens (Figure 5).

The power of detection of cancer by $^1$H-MRS was investigated by comparing the sensitivity, positive predictive value and accuracy among the 12 sections of the prostate peripheral zone (Figure 6). Examination of the total prostatectomy specimens revealed the presence of malignancy in 71 sections in 10 patients: biopsy detected malignancy in 31 of these sections while $^1$H-MRS detected malignancy in 43 of them. The sensitivity of detection was thus 43.7% with biopsy compared to 60.6% with $^1$H-MRS ($p<0.001$). Combining the results of biopsy and $^1$H-MRS increased the sensitivity of detection up to 88.7% ($p<0.001$ vs. biopsy, and $^1$H-MRS alone). Examination of the total prostatectomy specimens revealed the presence of malignancy in 31 of the 44 sections in which biopsy had detected malignancy and in 43 of the 49 sections containing malignancy detected by $^1$H-MRS. Therefore, the positive predictive value was 68.9% with biopsy and 87.8% with $^1$H-MRS, which indicated that $^1$H-MRS had a higher positive predictive value than did biopsies. The combination of the findings obtained by biopsy and $^1$H-MRS indicated malignancy in a total of 70 prostate sections, and 63 of those sections also showed malignancy in the examination of the total prostatectomy specimens. Therefore, the positive predictive value was 88.7% with the combination of biopsy and $^1$H-MRS (Figure 6). The accuracy was 54.6% with biopsy, 71.4% with $^1$H-MRS and 87.4% with the combination of these two diagnostic modalities.

**Discussion**

At present, prostate biopsy is the only definitive means for the diagnosis of prostate cancer, with significant morbidity and mortality. In addition, false-negative results require repeated biopsies. Literature reports that around 30% of cancers are detected in the second biopsies (21). Current imaging modalities are not satisfactory enough to support biopsies. Our present study was thus designed and carried out to elucidate whether the combined use of $^1$H-MRS and biopsy improve the accuracy of identifying the localized distribution.

We first established a cut-off value for the CCr ratio in prostate cancer. Previous reports have determined the cut-off value as a value exceeding the mean $+2$ SD of the CCr ratio for noncancerous prostate tissue (14, 22). By applying the same principle, a cut-off value for the CCr ratio in this study included no false-positives sites and only one false-negative site (Figure 4).

In our study, the sensitivity, positive predictive value and accuracy were all significantly higher with $^1$H-MRS alone than with biopsy alone. Moreover, with the combination of $^1$H-MRS and biopsy each of the sensitivity, positive predictive value and accuracy was further increased. The combined application of $^1$H-MRS and biopsy was thus proposed to be a good method for improving the accuracy of diagnosis of localized prostate cancer. More practically, this approach allows the clinician to consider performing targeted biopsy of the prostate only at the regions that are found to be $^1$H-MRS-positive (23), or re biopsy of sections found to be $^1$H-MRS-positive but biopsy-negative.

Scheidler et al. (14) divided total prostatectomy specimens into sextants and found that with MRS the ranges of values in each section were 63–86% for the sensitivity, 49–75% for the specificity, 77–83% for the positive predictive value, 51–65% for the negative predictive value and 67–74% for the accuracy. Wefer et al. (24) similarly divided total prostatectomy specimens into sextants and compared the findings with those of sextant prostate biopsy, MRI and MRS. They reported that the sensitivity of MRS was the highest (MRI 67%, MRS 76% and biopsy 50%), whereas its specificity was the lowest (MRI 69%, MRS 68% and biopsy 82%). However, both of those research groups carried out their investigations on the premise of sextant biopsy based on division of the peripheral zone of the prostate into six sections, whereas today the recommendation is to use a biopsy core number of at least eight (25). Our present study is the first reported use of at least 10 cores and comparison of the diagnostic capacities of biopsy and MRS, and it is also the first documentation that addition of MRS to biopsy is useful for diagnosing localized prostate cancer.

$^1$H-MRS is a diagnostic modality that is based on in vivo metabolic information, and for this reason it provides information that differs from the information obtained with conventional MRI. Several lines of evidence show that $^1$H-MRS would be useful for detecting tumors even after administration of hormonal therapy (22) or radiotherapy.
(26) without the signal intensity being affected. The limitation of $^1$H-MRS in this study was the use of the endorectal coil. It has been reported that endorectal coil increases diagnostic ability, (1, 5, 15, 26) but it places considerable stress on the patient. Moreover, it has been reported that it is often difficult to differentiate cancer from benign hyperplasia in the transition zone in MR imaging, even when the endorectal coil is used (27), which negates the application of $^1$H-MRS in the transitional and central zones. The capability of the spatial resolution of the endorectal coil is lowered in the transition zone by the distance from the coil. Further modalities to circumvent endorectal coils warrant further studies.

In conclusion, $^1$H-MRS resulted in better accuracy in the diagnosis of prostate cancer than biopsy alone for the peripheral zone of the gland. $^1$H-MRS together with biopsy might improve the diagnostic accuracy and the location of primary carcinomas.

References


