
● *Original Contribution*

IN VIVO DIFFERENTIAL DIAGNOSIS OF PROSTATE CANCER AND BENIGN PROSTATIC HYPERPLASIA: LOCALIZED PROTON MAGNETIC RESONANCE SPECTROSCOPY USING EXTERNAL-BODY SURFACE COIL

JONG-KI KIM,* DUK-YOUN KIM,† YOUNG-HWAN LEE,* NAK-KWAN SUNG,* DUCK-SOO CHUNG,*
OK-DONG KIM,* AND KAP-BYUNG KIM†

Departments of *Radiology and †Urology, School of Medicine, Catholic University of Taegu-Hyosung, Taegu, Korea

Localized proton-stimulated echo acquisition mode (STEAM) spectroscopy was performed in seven patients with benign prostatic hyperplasia (BPH), six patients with prostate cancer, and seven healthy volunteers to determine whether citrate levels detected using a saddle-type external-body surface coil (two loops of 13 cm × 17 cm) could reliably discriminate BPH from prostatic cancer. Relative area ratios of citrate level to choline plus creatine or citrate to lipid signal were compared with postoperative pathologic histology findings. The metabolic signals were well detectable as much as the line width of water resonance was ranging from 5 to 9 Hz. Average SNRs of citrate in BPH and prostate cancer were 11.4 and 1.9, respectively. The major finding was consistently lower citrate levels in prostate cancer compared with BPH and normal prostate central gland. This was significantly ($p < 0.01$) reflected by lower mean citrate/[creatine+choline] peak area ratio and citrate/lipid peak area ratio observed for region of cancer (0.446 ± 0.063 , 0.097 ± 0.030) compared with BPH (1.458 ± 0.107 , 0.786 ± 0.162) and normal central gland (1.418 ± 0.129 , 0.175 ± 0.011), respectively. These studies demonstrate the potential of citrate spectrum detected by an external-body surface coil as an in vivo marker for discriminating prostate cancer from BPH. © 1998 Elsevier Science Inc.

Keywords: In Vivo MRS; Citrate; BPH; Prostate cancer; External surface coil.

INTRODUCTION

Prostate cancer is now the most common cancer amongst the male population in the Western world and the second leading cause of cancer death.¹ At the present time, PSA remains the most important and useful marker for monitoring prostate cancer, although its sensitivity and specificity still leave something to be desired.² In prostatic cancers, MRI techniques have proved to be comparable if not superior to other modalities, such as computerized tomography and transrectal ultrasonography, in determination of the local extent of cancer.^{3–5} However, it is difficult to use this modality in screening of patients for cancer and differentiate consistently between benign prostatic hyperplasia (BPH) and cancerous nodules or between those cancers that will progress and metastasize and those that will remain latent.^{6–8} Magnetic resonance spectroscopy (MRS) studies have even more potential

than MRI studies because of the ability of MRS to assess noninvasively biochemical parameters of tissue in vivo. A series of research using animal models,⁹ cell lines,¹⁰ and tissue extracts^{9,11–13} have established that prostatic tissue citrate can be a marker for the differentiation of BPH from prostate cancer. The recent investigations of localized proton¹⁴ and phosphorous¹⁵ spectra or proton spectroscopic imaging¹⁶ of the human prostate using endorectal coils have shown the feasibility of differential diagnosis between BPH and cancer based on citrate level and phosphate metabolites. Formerly magnetic resonance spectroscopy of the human prostate gland using conventional surface coils placed outside body was technically not feasible. This was because the small size and deep location of the prostate preclude acquisition of good signal-to-noise magnetic resonance spectra. Recently, other groups reported successful acquisition of volume

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Address correspondence to Jong-Ki Kim, Ph.D., Department of Radiology, School of Medicine, Catholic University of

Taegu-Hyosung, 3056–6 Taemyung 4-Dong, Taegu, Korea.
E-mail: jkkim@cuth.cataegu.ac.kr

selective proton spectra of human prostate with a commercial Helmholtz-type surface coil (Siemens)¹⁷ or pelvic-phased array coil,¹⁸ in which citrate spectra were comparable to spectra acquired with endorectal coils. It is handy to acquire signal using an external coil without regard to patient's tolerance and without need of pre-enema. In this study, we used a saddle-type flexible surface coil (General Electric Medical system), which was tightly secured over the pelvic area to receive signal, and performed localized proton MRS to investigate whether metabolic signal including citrate discriminate BPH from cancer. This study presents the potential of external-coil spectrum of prostate citrate for differential diagnosis between BPH and cancer which had been formerly regarded as difficult.

MATERIALS AND METHODS

Patients

A total of 20 patients and volunteers were studied, including six patients with prostate cancer, seven patients with only benign prostatic hyperplasia, four healthy young volunteers and three healthy old volunteers as age-matched control. Young volunteers chosen were 25 to 28 years of age, since it is known that pathologic changes of BPH first begin after age 40 years.¹⁹ Volunteers were confirmed by history and physical examination to have no known urologic disease and specially no history of prostate disease or voiding problems. Patients with BPH were 55 to 83 years of age awaiting transurethral prostatectomy (TURP) from clinical indications. Transrectal ultrasound with biopsy showed no evidence of cancer, and BPH was confirmed by low urine flow rate (less than 10 ml/s) and pathologic examination of transurethral resected tissues (nodular hyperplasia). Six patients, 72 to 79 years of age, had biopsy-proven prostate cancer, serum prostate-specific antigen (PSA) values ranging from 68.64 to 176.53 ng/ml. All cancer patients underwent transurethral resection and hormonal therapy. All MRS were performed before biopsy and TURP.

Imaging and Spectroscopy

All studies were performed on a 1.5 Tesla Signa clinical imager using a flexible surface coil (General Electric Medical System, Milwaukee, WI, USA) to receive and body coil to transmit. The Signa general purpose (GP) flex coil design is a linear, receive-only flexible coil, which consists of two 13 cm × 17 cm loops that are serially connected to a corotating "saddle coil" pair, configured to form a figure 8 coil circuit. Coil was secured over the pelvic area of patients in supine position. Localizer image using breath-hold fast-Spoiled Gradient (SPGR) (80°, 12 ms, 100 ms; flip angle/TE/TR) and T2-weighted fast spin echo (4000 ms/90 ms; TR/TE)

images were acquired with field of views 16 to 24 cm in sagittal and axial orientation, respectively. Volume selection for acquiring spectrum was performed by stimulated echo acquisition mode (STEAM), with a TE of 30 ms and a TR of 500 ms. For cancer patients, the localization of mass was guided by previous determination from ultrasonogram and was additionally confirmed using T2-weighted imaging in some cases. Magnetic field homogeneity of the localized volume was optimized by shimming water resonance via Automatic Prescan (up to second order correction) and additional manual shimming. Obtained line width of water signal were typically within range of 5–9 Hz. Water suppression was achieved by exciting and dephasing the water signal with three chemical-shift-selective (CHESS) radiofrequency pulses and corresponding crusher gradients applied before STEAM localization sequence was begun. Water suppression was effectively more than 99%. To obtain localized 1H spectra to measure tissue citrate levels in the in situ human prostate, we performed STEAM spectroscopy with volume selection (typically 2.02–2.73 cc).²⁰ Spectra were acquired from 128 to 256 averages, depending on voxel size, with a TE of 20 ms, a TM of 32.4 ms, and a TR of 2.0 s or 2.5 s, yielding a total acquisition time of between 5 and 10 min. Total examination time including localizer imaging, shimming and patient handling was between 20 min and 30 min. Echo time (TE) and mixing time (TM) were taken by considering J-coupled citrate AB spin system ($J = 15.4$ Hz) as discussed by previous investigators.²¹ Before Fourier transformation, time domain data were zero-filled to 2048 points and apodized with exponential multiplication with 1 to 2 Hz line broadening, and plotted with baseline correction if necessary, and referenced to water at 4.77 ppm. In vivo citrate levels are reported as ratio of the citrate peak area with the sum of the areas of the choline and creatine peaks and ratio of the citrate peak area to the lipid peak area. Metabolic peak areas were determined with SAGE (General Electric Medical system, USA) software. Outer peaks of citrate multiplet were not included in peak integration since those peaks were not resolved clearly. Comparison of citrate peak area ratios between cancer, BPH and normal central gland was made using Kruskal–Wallis test for multiple comparisons. Differences between means were considered to be significant for $p < 0.01$.

Phantom Studies

60 mM citric acid solution was prepared in 100-ml bottle container, which was placed in a beaker containing one liter of 2% agarose gel as a prostatic phantom for comparison study of endorectal-coil acquisition and external-coil acquisition. In the external-coil acquisition using GP flexible coil, 9 cm was chosen as typical

distance between selected voxel and center of surface coil, while 2.5 cm was selected in the endorectal-coil acquisition. Water-suppressed STEAM method was performed on a selected voxel ($13 \times 13 \times 15 \text{ mm}^3$) with signal averaging of 64 excitations. All other acquisitional parameters were identical with those of *in vivo* acquisition.

RESULTS

The citrate signal was well detectable as shown in Fig. 1, which appeared comparable with the published endorectal spectrum from other investigators. Average SNR of citrate for a 256 acquisition was 8.7 ± 3.2 in the normal central gland. Corresponding SNRs in BPH and cancer patients were 11.4 ± 4.3 and 1.9 ± 1.3 , respectively. In multipulse sequences, the strongly coupled protons of citrate exhibit signal losses and phase distortions due to coupling effect.¹⁷ In comparison with uncoupled nuclei, they also respond differently to flip angle variations, which are caused by shaped pulse or the use of surface coils. We used same acquisition parameters, TE (20 ms) and TM (32.4 ms), as used in previous STEAM spectroscopy study by other authors¹⁴ to check out whether or not we see metabolic signals like in endorectal spectrum.

The spectra in Fig. 1 are representative water-suppressed ^1H STEAM spectra from the region of a prostate cancer, BPH nodule of a BPH patient and normal central gland of a healthy volunteer. Citrate, labeled as C, has a distinctive peak resonating at 2.68 ppm that does not overlap other peaks in *in vivo* proton spectra of the prostate. In contrast, choline, creatine, and amino acid labeled as A, B, D, respectively are composite arising from multiple metabolites. Three 5-mm thick axial, T2-weighted (4000 ms/100 ms) FSE images corresponding to the center of the spectroscopic voxels are shown in Fig. 2.

Table 1 reveals that significantly ($p < 0.01$) lower citrate to choline plus creatine area ratios or citrate to lipid area ratios were observed for the region of cancer (0.446 ± 0.063 , 0.097 ± 0.030 , respectively) compared with BPH (1.458 ± 0.107 , 0.786 ± 0.162) and normal central gland of young control (1.418 ± 0.129 , 0.175 ± 0.011). Corresponding area ratios for age-matched control group were 1.436 ± 0.164 and 0.268 ± 0.085 . There was no overlap of individual cancer and control citrate ratios (Fig. 3). Additionally, there was no overlap of BPH and cancer ratios. Both cancer and BPH demonstrated an increase in the choline resonance relative to central gland of control. But increase in choline relative to creatine resonance was more pronounced in prostate cancer compared with BPH in which this increase was not observed in some cases.

Increased choline signal in cancerous prostatic tissue is parallel with the observation of brain tumor spectrum.

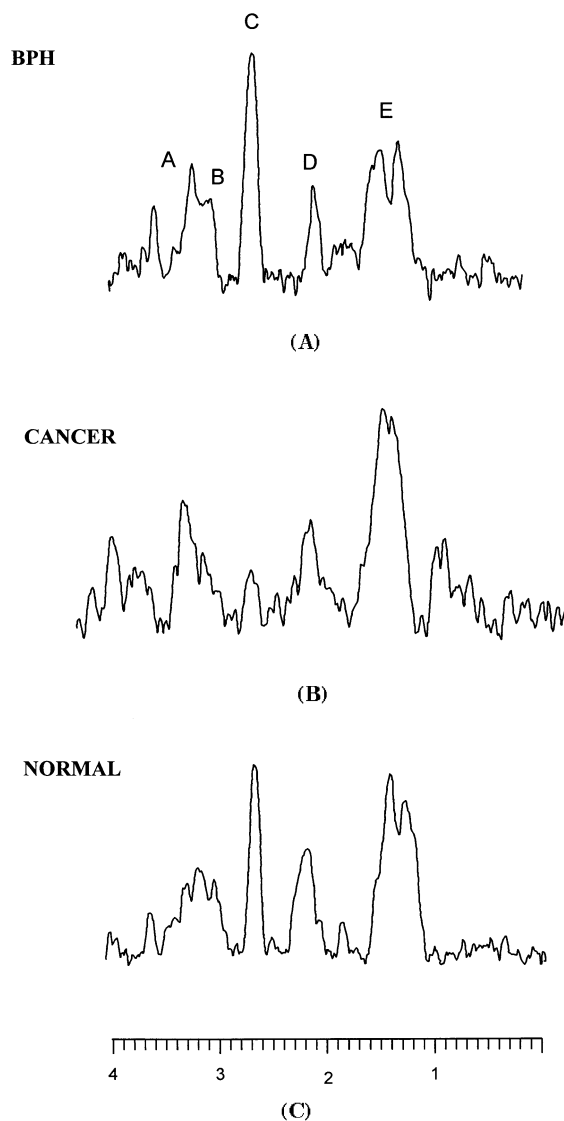


Fig. 1. Typical water-suppressed ^1H STEAM spectra of BPH (A), prostate cancer (B), and normal prostate (C). In A: A, choline; B, creatine; C, citrate; D, amino acids; E, lipid. Citrate increase in BPH spectrum is contrasting to decrease in prostate cancer spectrum.

In this study, the distinction among cancer, BPH, and normal central gland of control appeared conspicuous in the citrate to lipid area ratio rather than in the citrate to choline plus creatine ratio as shown in Table 1. Presence of mobile lipid in human prostate tissue had been controversial with contamination from surrounding structures. Recent *ex vivo* NMR study showed existence of lipids in high-resolution proton spectra of BPH and cancer tissue while tissue extracts spectra showed no lipids which might be subject to degradation during preparation.²² Resonances near 1.0 and 3.9 ppm in spectrum (b)

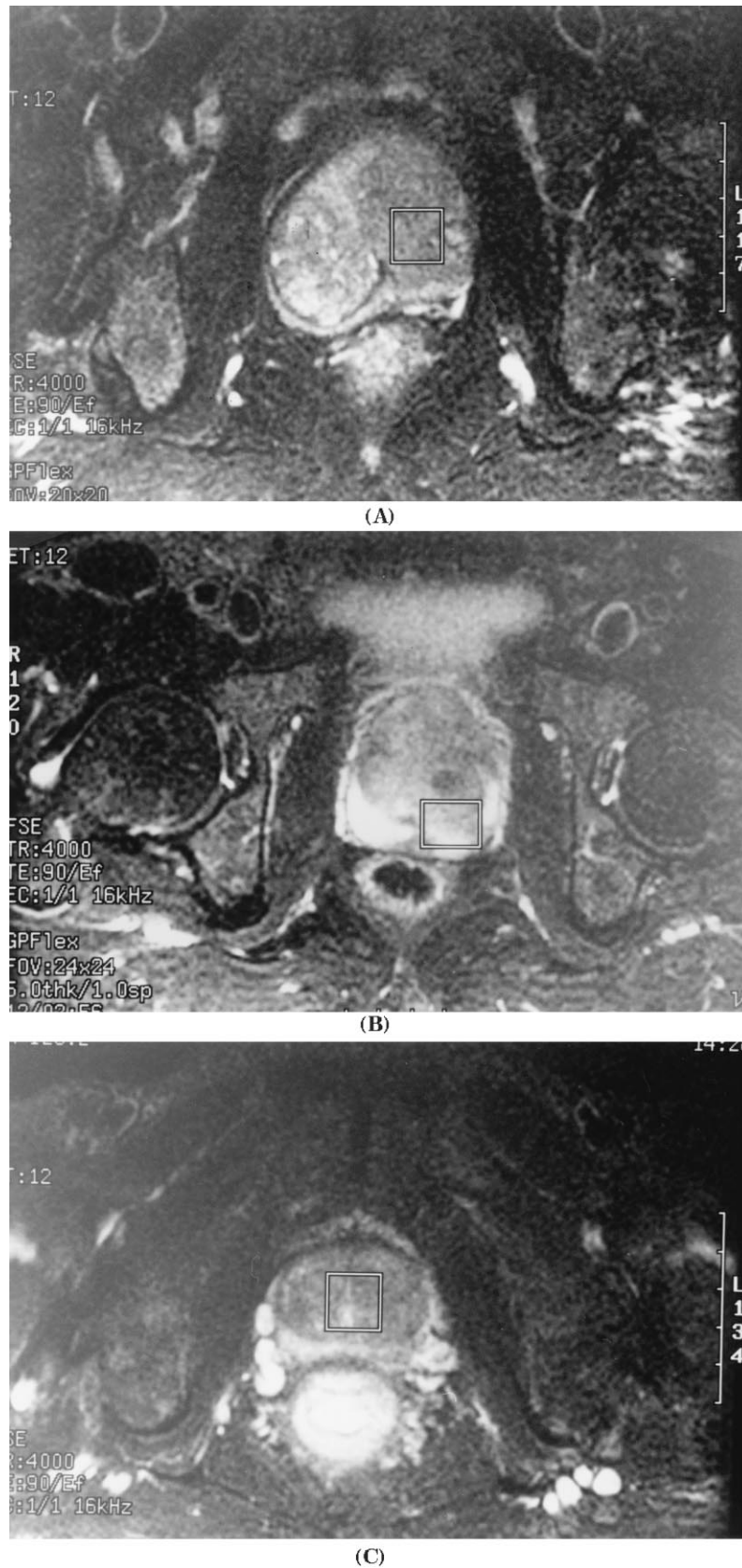


Fig. 2. Representative T2-weighted axial FSE images and spectroscopy voxel (square) of BPH (age: 68, $12.5 \times 12.5 \times 13 \text{ mm}^3$; A), prostate cancer (age: 72, $13.5 \times 11 \times 13 \text{ mm}^3$; B), and normal prostate (age: 28, $13 \times 13 \times 13 \text{ mm}^3$; C) in typical examination.

Table 1. Prostatic tissue citrate level

	Citrate/(choline + creatine)†	Citrate/lipid	Citrate‡
BPH (<i>n</i> = 7)	1.458 ± 0.107	0.786 ± 0.162	11.4 ± 4.3
Cancer (<i>n</i> = 6)	0.446 ± 0.063	0.097 ± 0.030	1.9 ± 1.3
Normal CG (<i>n</i> = 4)	1.418 ± 0.129	0.175 ± 0.011	8.7 ± 3.2
Age-matched Control CG (<i>n</i> = 3)	1.436 ± 0.164	0.268 ± 0.085	

* Citrate peak/[A + B] area ratio ±SD; †: averaged SNR of citrate peak itself, CG: central gland.

were not observed consistently in all spectra. But resonance near 3.7 ppm, presumably inositol, was observed in most patient spectra. In some cancerous prostatic tissues the choline and creatine resonance were very small. In particular all tissue signals except lipid were extremely small in the postsurgery spectrum of one cancer patient as shown in Fig. 4.

Figure 5 shows STEAM spectra of selected voxel in phantom using endorectal-coil and external-coil where SNR of endorectal citrate spectrum (37.7) was 1.87 times larger than that of external citrate spectrum (20.17).

DISCUSSION

Unlike former investigations with endorectal coils, we used a flexible surface coil consisting of two identical loops (13 cm × 17 cm) placed outside body for signal reception. Magnetic field homogeneity in the selected volume was obtained by automatic shimming procedure and additional manual shimming with water resonance signal. Obtained line width of water signal was in the range of 5 to 9 Hz, which seemed to be comparable with endorectal spectra reported from other authors.^{14,17} Generally SNR was excellent in all patients although it was compromised in comparison with endorectal coil. As shown in phantom studies overall sensitivity of external-coil acquisition was not very small (53%) even though the distance for receiving signal was 3.6 times larger than that in endorectal acquisition. Therefore at a TE of 20 ms and a TM of 32.4 ms, the citrate signal was well detectable without showing fast phase modulation. Since flexible coil used in this study actually was wrapped over the pelvic area of patient, signal sensitivity may be subject to variation depending on the patient size. However, we did not evaluate those effects on S/N systematically because of lack of adequate patients. Average citrate concentrations are about 60 mM in the central gland and peripheral zone.^{17,23} Citrate synthesis and secretion are exocrine functions in the prostate which are stimulated by androgenic hormone. The decreased citrate in prostate cancer is due to diminished capacity to synthesize and secrete

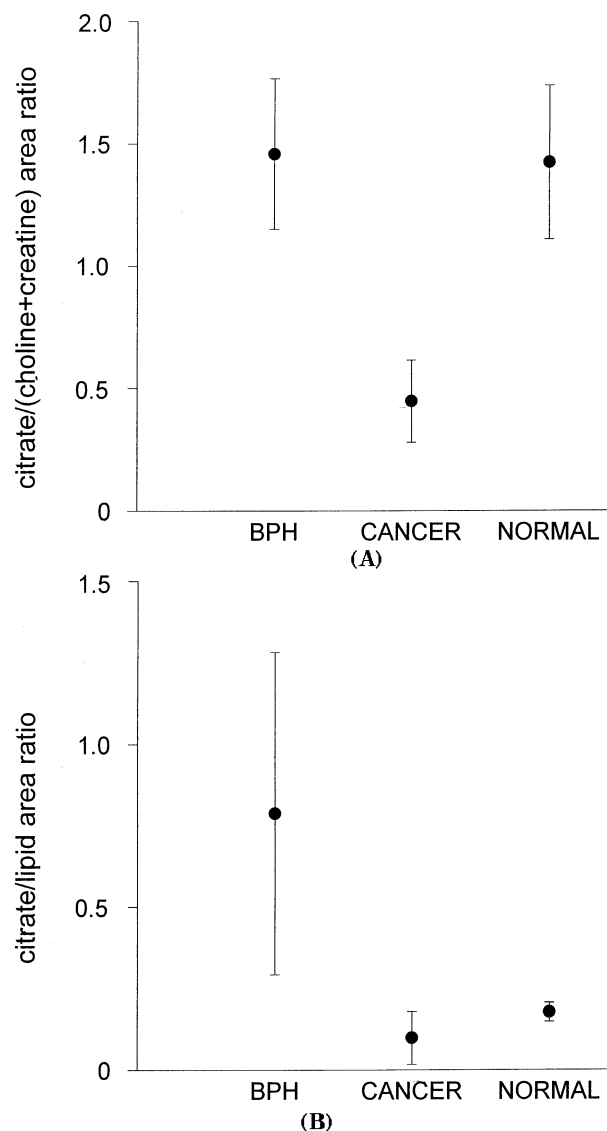


Fig. 3. Plot of citrate/[creatine plus choline] area ratio (A) and citrate/lipid area ratio (B) for regions of prostate cancer, benign prostatic hyperplasia (BPH), normal central gland in volunteers, and age-related patients.

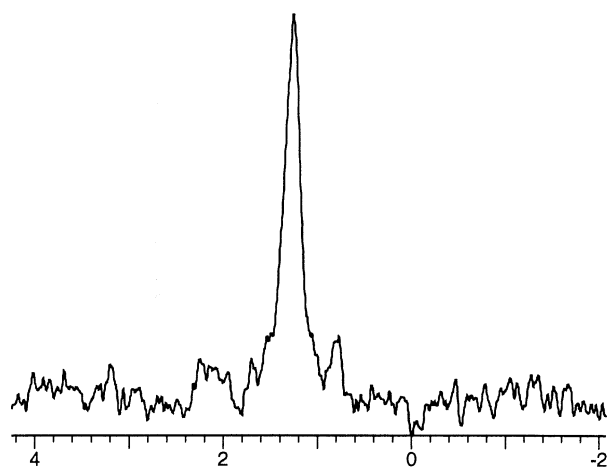


Fig. 4. ^1H STEAM spectrum of a prostate cancer after surgery.

citrate, subsequently malignant epithelial cells occupy areas normally occupied by glandular ducts.^{23,24} In the T2-weighted FSE image, cancer region was hypointense compared with normal or BPH prostate. This is somewhat unusual because tumors elsewhere in the body are generally hyperintense to their organ of origin on T2 weighting. This decrease in signal intensity was reported to be correlated with the histomorphologic finding of a net decrease in luminal spaces.¹⁴ Hormone therapy was known to cause prostatic epithelial cells to atrophy and

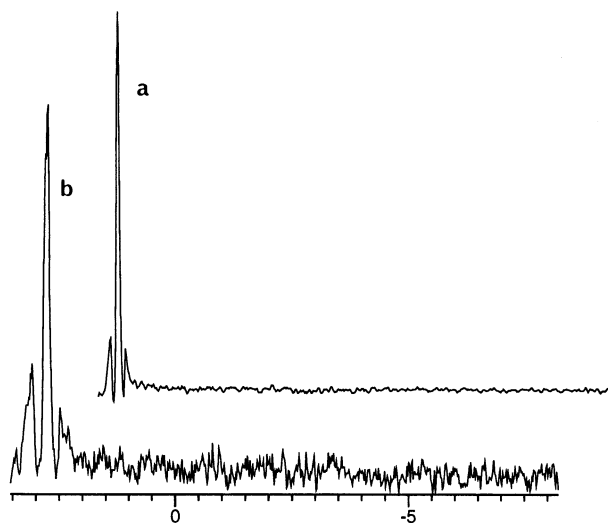


Fig. 5. Comparative plot with same relative vertical scale a) endorectal- and b) external-coil spectra of a phantom containing 60 mM citric acid. Distance between acquiring voxel and center of receiving coil was 2.5 cm in endorectal acquisition and 9 cm in external acquisition, respectively. SNR of endorectal acquisition was 1.87 times higher than that of external acquisition at the designated measuring distance.

die, which might be reflected in decreased citrate in *in vivo* ^1H prostate spectra.²⁵ In this study cancer stage of all patients were higher than Gleason score 7, and MRS were done just after starting hormonal therapy. Hence, those effects were not considered in this study. Spectral variation of prostatic cancer depending on tumor stage and therapy is presently under investigation. A preliminary data showed depletion of tissue signals except mobile lipids after surgery of prostatic cancer (see Fig. 4). Elevated level of choline-containing metabolites in ^1H spectra of prostate cancer was consistent with previous observations of high levels of phosphomonoesters by using endorectal coils,¹⁵ indicating increased rate of cell proliferation. In addition, the increase of mobile lipids in cancer patients may be reflected in large decrease of citrate to lipid ratio compared with in BPH patients. Amino acids resonance was not specifically variable for distinguishing cancer from BPH in this study.

Zonal dependence of distribution of citrate signal may be reflected in the variation of citrate to other signal area ratio in pathologic prostatic tissue of patients and normal central gland of volunteers. Citrate is more fluent in the peripheral zone than in the central gland area.¹⁸ This trend was positively correlated with advancing age.¹⁸ It was shown that citrate in the central gland area was not much variable with advancing age. In this study of some BPH patients, SNR for citrate in the peripheral zone was higher than in central gland. But we did not evaluate zonal distribution of citrate in all BPH patients. This is currently under investigation using spectroscopic imaging method with same coil as used in this study. Citrate to choline plus creatine area ratio was not distinguishing between BPH and normal central gland as shown in Table 1. However obtained average SNR of citrate peak itself discriminated BPH (11.4 ± 4.3) from normal central gland (8.7 ± 3.2). Citrate to lipid area ratio also resolved this ambiguity. It was of higher value in BPH (0.786) than was in normal central gland (0.175). Previous biochemical studies *in vitro* have demonstrated a decrease in citrate content in adenocarcinoma of prostate and an increase in BPH.²⁶ Although citrate decrease in adenocarcinoma was well reflected in the area ratio of citrate to choline plus creatine peaks, but an increase in BPH was not well reflected in this area ratio with large variation in BPH patients. Composite peaks of choline and creatine without good resolution can be subject to integration error, giving large variation to the area ratio of citrate to choline plus creatine peaks. We think quantitative study of citrate would more accurately reflect citrate increase in BPH than relative area ratio to other composite peaks as indicated in recent study by other group.²⁷ This approach will be pursued in future study.

CONCLUSION

External-coil spectra of prostate citrate demonstrated potential to reliably discriminate between BPH and prostate cancer with good SNR of metabolic signals. Decreased citrate level in the region of cancer was reflected in the area ratio of citrate to choline plus creatine peaks, which distinguish significantly ($p < 0.01$) between BPH and prostate cancer. Increased citrate in BPH tissue in comparison with normal central gland was not reflected in the area ratio of citrate to choline plus creatine peaks but in the obtained average SNR of citrate itself, distinguishing BPH (11.4 ± 4.3) from normal central gland (8.7 ± 3.2). In addition the area ratio of citrate to lipid peak was different ($p < 0.05$) between BPH nodule and normal central gland.

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