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Differentiation Diagnosis of Hypo-Intense T2 Area in Unilateral Peripheral Zone of Prostate Using Magnetic Resonance Spectroscopy (MRS): Prostate Carcinoma versus Prostatitis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: To determine whether magnetic resonance spectroscopy (MRS) can be used as a reliable denominator for the differentiation of prostatitis and prostate cancer (PCa) in the peripheral zone.

Material/Methods: Forty-three patients with unilateral peripheral zone PCa and 35 patients with unilateral peripheral zone prostatitis were recruited for this study. Magnetic resonance imaging (MRI) and MRS were acquired on a 1.5T MR scanner. The ratios of (Cho+Cr)/Cit of hypo-intense T2 area were calculated. The mean ratios of (Cho+Cr)/Cit in hypo-intense T2 area of PCa and that of prostatitis were compared retrospectively by *t*-test. The citrate and choline amplitudes in the hypo-intense T2 area were compared with that in the contralateral normal peripheral zone tissue.

Results: The mean ratios of (Cho+Cr)/Cit in the hypo-intense T2 area of PCa was 3.0±2.48, whereas that of prostatitis was 5.2±7.08, without significant statistical difference (p=0.306). A reduction in citrate was seen in both PCa and prostatitis tissue, however, choline was elevated in PCa tissue, whereas on the contrary, choline had no significant change in cases of prostatitis.

Conclusions: The mean ratios of (Cho+Cr)/Cit had no specificity in differentiation of PCa and prostatitis in the peripheral zone, however, the metabolic pattern showed promise as an adjunct to conventional imaging in differentiating prostatitis from PCa in the peripheral zone.

MeSH Keywords: Magnetic Resonance Imaging • Magnetic Resonance Spectroscopy • Prostatic Neoplasms • Prostatitis

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Background

Prostate cancer (PCa) and prostatitis are most often encountered in elderly men. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have become important tools in the discrimination of prostatic hyperplasia and PCa. However, their ability to differentiate PCa from prostatitis can be difficult. Radiologists often face the dilemma of how to diagnose a patient in whom there is a high suspicion for PCa based on a low signal area of the peripheral zone (PZ) on T2-weighted MR imaging (T2WI), in which the malignant changes usually appear as a hypo-intense signal compared to normal-appearing PZ [1]. However, the diagnostic value of anatomic T2WI in discriminating PCa from prostatitis has been limited, for low signal intensity (SI) is not specific for PCa. Prostatitis exhibits the same low SI area on T2WI in the same predilection site for the PZ [2]. Furthermore, it may demonstrate metabolic abnormality on MRS [3]. Meanwhile, both PCa and prostatitis are often accompanied by elevation of serum prostate-specific antigen (PSA) [4]. Thus, prostatitis can mimic malignancy and can lead to false-positive diagnosis of cancer [5,6]. Therefore, discriminating PCa from prostatitis in the PZ is a major challenge for the radiologist.

Recent research has focused predominantly on PCa detection, which has been revolutionized by multi-parametric magnetic resonance imaging (mpMRI) [7]. In several studies, prostatitis can be differentiated from PCa using PI-RADS. However, prostatitis is indistinguishable from PCa using mpMRI in some cases, only a higher PI-RADS score can reliably differentiate between prostatitis and PCa since there is significant overlap between the two entities. Thus PI-RADS is only suitable to a limited extent for the primary assessment of prostatitis [8,9]. To our knowledge, a dedicated study comparing ^{1}H MRS characterization of prostatitis and PCa has not been reported. Therefore, the purpose of this study was to analyze and compare ^{1}H MRS of prostate cancer and prostatitis in the PZ and to determine if prostatitis and PCa in the PZ can be distinguished by MRS.

Material and Methods

This was a retrospective analysis utilizing the institutional prospective database at our hospital. Our local institutional review board approved the study and the need for additional institutional review board approval and informed consent was waived.

Patients

From July 2008 and September 2015, a total of 78 patients were enrolled in this study: 43 patients had PCa (average age 70 years; range, 53–82 years), 35 patients had prostatitis (average age 61 years; range, 37–79 years). The mean level of prostate-specific antigen (PSA) of all the patients was 12.9 ng/mL. All patients successfully underwent routine MRI and 3D MRS before prostate biopsy.

The inclusion criteria for prostatitis were as follows: TRUS-guided biopsy proved prostatitis at our institution within one week after MRI. Bacteria were found in cultures from prostatic fluid. The elevation of serum PSA returned quickly to normal range following antibiotic treatment.

The inclusion criteria for PCa were as follows: TRUS-guided biopsy revealed PCa at our institution within six months after MRI.

We excluded patients with: 1) prior prostate cancer treatment, or prior antibiotic treatment; 2) artifacts on MRS; and 3) lesions not located in the PZ.

MR imaging protocol

All examinations were performed on a 1.5-T system (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany), using the body coil for rf excitation and an integrated pelvic phased-array coil for acquisition. Transverse T1WI (700/12, FOV of 24×24 cm, 5-mm-thick sections, 1-mm section gap, matrix size, 256×192, and two signals acquired) were obtained and then T2WI (TR4300ms, TE97ms, FOV of 20×20 cm, section thickness 3.0 mm, intersection gap 0.6 mm, 230×256 matrix, and four signals acquired) were performed in three planes.

3D-^{1}H MRSI

3-D MRS examinations were performed using a body coil. After anatomical images of axial, coronal and sagittal were acquired, the examiner positioned the VOI of the MRS examination on the images showing the largest diameter of the prostate in all three planes. 3-D chemical shift imaging spectroscopy (3D CSI) sequence (TR690ms, TE120ms, FOV, 8×8×8 cm, times of collection six, matrix 12×12×12) was used in all patients. Water and fat signals were suppressed with outer volume saturation slabs. Presats (sat-bands) were positioned in all directions around the prostate in order to eliminate disturbances of the spectra caused by peri-prostatic tissue, fat tissue, and rectum tissue. The local magnetic field homogeneity was optimized with auto-shim procedure. The scan for the spectroscopy lasted approximately 8 to 10 minutes.

Data interpretation

T2WI analysis

We used a commercial PACS workstation (UniSight (EBM-PACS), Taiwan) to correct all images for the reception profiles of the pelvic phased-array coils. Images were analyzed in consensus by two radiologists with 17 years (ZTH) and 28 years (HCH)

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Table 1. Differentiation between prostatitis and prostate cancer.

	Prostate cancer	Prostatitis
Patients	43	35
Age (mean)	70	61
(Cho+Cre)/Cit (mean ±SD)	3.0±2.48*	5.2±7.08
Citrate peak	↓	↓
Choline peak	↑	No significant change

(Cho+Cre)/Cit indicates the mean ratio of (choline+creatine)/citrate; ↓ – decreased compared with contralateral normal peripheral zone tissue; ↑ – elevated. * p=0.306, versus prostatitis.

of experience in prostate MRI. The entire prostate gland and surrounding tissue were evaluated on T2WI. The suspicious hypo-intense area that suggested inflammatory or cancer lesion was localized.

MR spectroscopic analysis

Post-processing was carried out immediately after the spectroscopy measurement incorporated with water reference processing, filter, zero-filling, Fourier transformation, baseline correction, phase correction, and curve fitting. Spectra from individual MRS voxels were analyzed via the manufacturer's software package (Spectroscopy). MRS data sets were excluded when there was artifact from peri-prostatic fat or low signal-to-noise ratio (SNR). In hypo-intense T2 area, the ratio of (Cho+Cr)/Cit was calculated in both inflammatory and cancerous tissue in the PZ. In addition to metabolite ratios, the citrate and choline amplitudes in hypo-intense T2 area were compared with that of the contralateral normal PZ tissue.

Statistical analysis

Data were analyzed by Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) software version 16.0. We calculated the mean standard deviation of the ratio of (Cho+Cr)/Cit of the two types of lesions. The two sample t-test was performed to determine whether the ratio of (Cho+Cr)/Cit of the two types of lesions differed significantly (two tailed p values). A p value of <0.05 was considered statistically significant.

Results

All carcinomas and prostatitis lesions showed focal or diffuse hypo-intensity on T2WI. The mean (Cho+Cr)/Cit ratio in cancerous region was 3.0±2.48, and for prostatitis tissue it was 5.2±7.08, the difference was not statistically significant (p=0.306) (Table 1).MRS showed decreased Cit concentration in prostatitis, whereas the peak of choline did not change significantly (Figure 1A–1F); on the contrary, the peak of choline in cancerous regions was significantly higher than the contralateral normal regions and the Cit concentration was significantly reduced than normal (Figure 2A–2F).

Discussion

MRS is a relatively new technique in PCa detection, but has been used in routine clinical practice since the early 1980s [10,11]. It has been shown to be effective in improving the accuracy of differential diagnosis of prostate diseases [12–15]. T2WI has been applied more often for the precise detection and staging of PCa [16]. MRS provides information about the cellular metabolites within the prostate gland by displaying the relative concentrations of key chemical constituents such as citrate, choline, and creatinine. The ratio of (Cho+Cr)/Cit has been used as a routine evaluation system [17]. Early studies revealed the ratio of (Cho+Cr)/Cit increased in malign tissue, whereas, a lower ratio of (Cho+Cr)/Cit can be found in benign tissue, for example, a higher ratio of (Cho+Cr)/Cit is found in cancer tissue than in benign prostatic hyperplasia tissue [18,19]. It was anticipated that the ratio of (Cho+Cr)/Cit might also be reduced in prostatitis tissue.

However, in our study this was not the case. The mean ratio of (Cho+Cr)/Cit for inflammatory tissue (5.2±7.08) increased significantly in our study. No significant difference was found between prostatitis and PCa (p>.05). The results of our present study demonstrated that the mean ratio of (Cho+Cr)/Cit was not suitable for differentiation between PCa and prostatitis. As shown in our study, the ratio of (Cho+Cr)/Cit increased in both prostatitis tissue and PCa tissue. So the ratio of (Cho+Cr)/Cit was not a specific marker for PCa; the overlap of the ratio of (Cho+Cr)/Cit hindered a reliable differentiation between the two histopathologic groups. Similar to other prior studies reported in the literature [20–22], PCa has been traditionally identified on the basis of elevated choline (Cho) and a ratio threshold of (Cho+Cr)/Cit of 0.5 or more. Prostatitis, however, in our prospective study did result in abnormal metabolic ratios. However, the ratio of (Cho+Cr)/Cit between the two groups was of no statistical significance.

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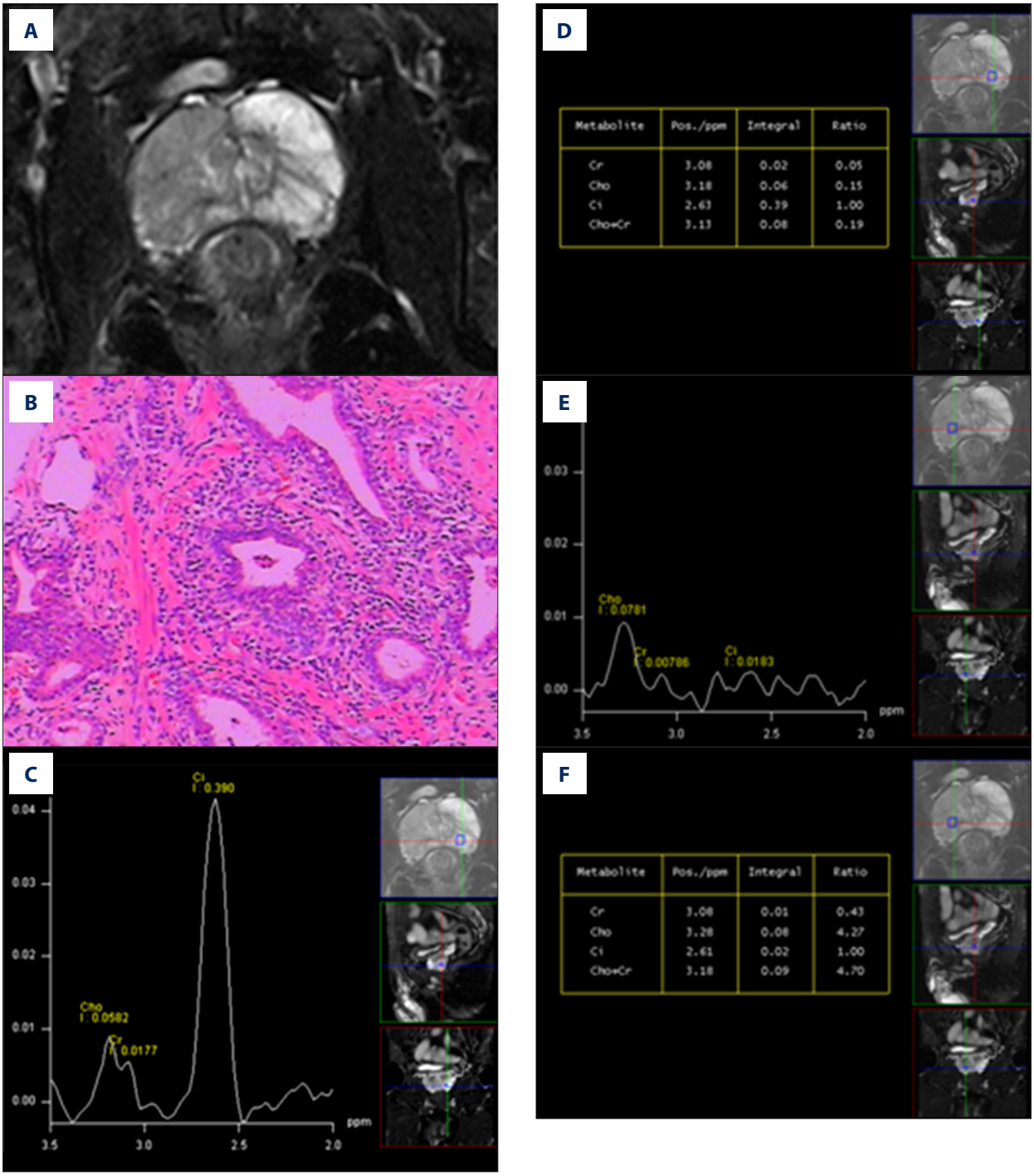

Figure 1. Magnetic resonance imaging (MRI), magnetic resonance spectroscopic imaging (MRS), and pathologic data in a 57-year-old patient with prostatitis (prostate-specific antigen level of 4.0 ng/mL), and histopathologic findings confirmed prostatitis. Transverse T2-weighted MR image shows a diffuse low intensity area in the right peripheral zone (**A**). Pathologic map (**B**) corresponds to MRI in **A** revealed inflammatory cell. The contralateral normal zone spectral shape (**C**) and CC/C value (**D**); voxels in **E** have MR spectral pattern of elevated choline and significantly reduced citrate. CC/C=4.70 (**F**). These findings mimic those of cancer; while compared to the contralateral normal district spectrum form, choline peak has no obvious change in prostatitis.

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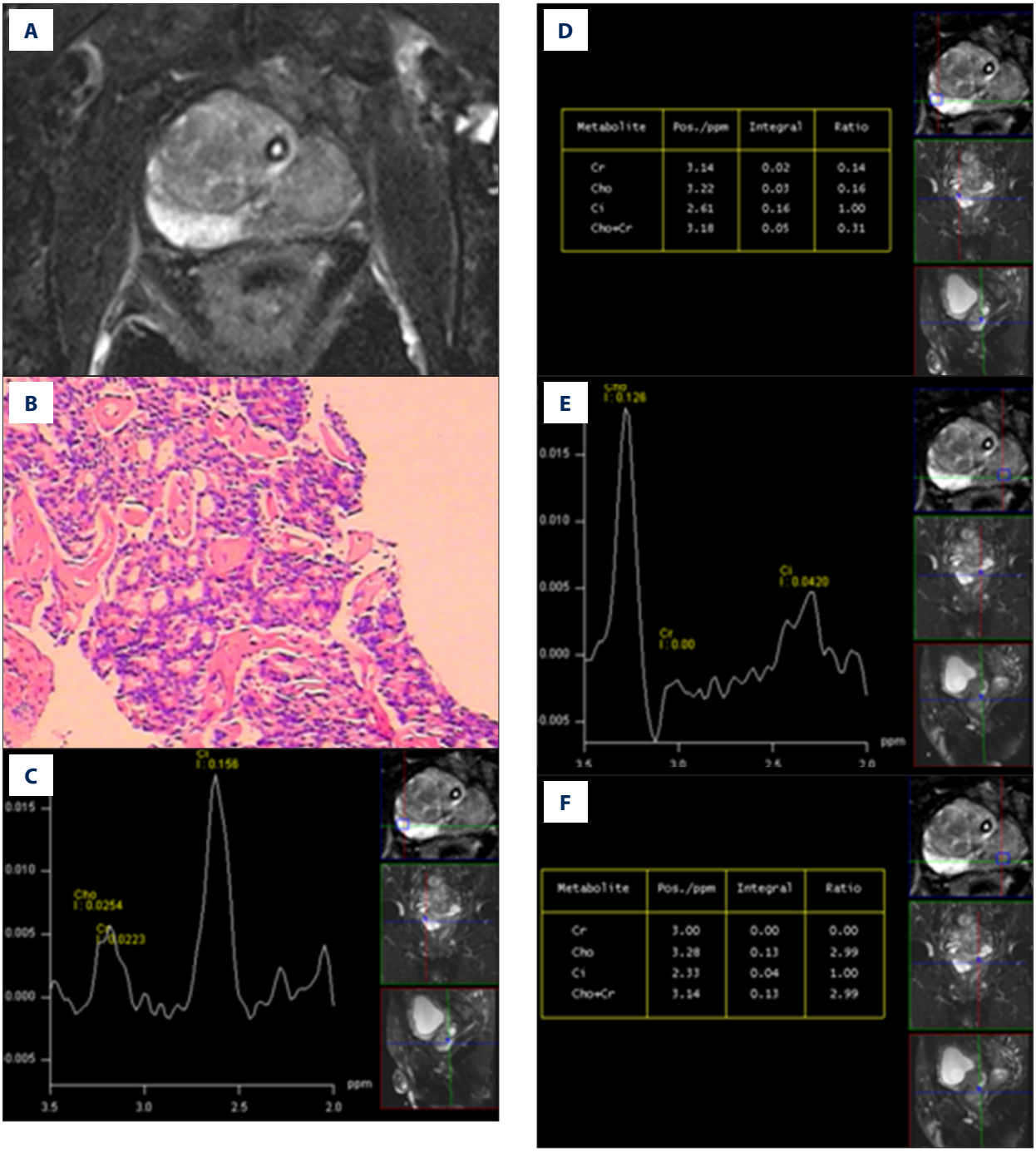

Figure 2. Magnetic resonance imaging (MRI), magnetic resonance spectroscopic imaging (MRS), and pathologic data in a 54-year-old patient with prostate cancer (clinical stage T2a, Gleason score of 6, and prostate-specific antigen level of 6.0 ng/mL). Transverse T2-weighted fast spin-echo MR image (**A**) shows low signal changes in left peripheral zone. Pathologic map (**B**) corresponds to MRI in **A**; biopsy confirmed the diagnosis of prostate cancer. No extracapsular extension. MR spectra from a voxel (blue square inset) in the right peripheral zone that contains healthy prostate tissue exhibits that the levels of citrate are much higher relative to choline (**C**); a voxel in the left peripheral zone that contains prostate cancer, this relative concentration is reversed (**D**). MRS showed significantly elevated choline and reduced citrate peaks (**E**). CC/C=2.99 (**F**), consistent with prostate cancer.

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In addition, our results revealed a significant reduction of Cit and elevation of Cho in cancerous regions, whereas the prostatitis lesions demonstrated normal levels of Cho and reduced or no Cit, when compared to the contralateral normal prostate tissue. It is well known that healthy prostate tissue demonstrates high levels of Cit and low levels of Cho [23–27]. The normal contralateral PZ provides the reference values of the Cho amplitudes and of the Cit amplitudes on profile MRS for MRS measurements of the pathologic PZ. This relative quantitative method was used to study certain metabolite changes [28]. The metabolic pattern, particular for Cho peak, was helpful for the differentiation of PCa and prostatitis in the PZ; Cho peaks higher than those in the corresponding normal regions, the greater the possibility of PCa.

The cause of the elevated ratio of (Cho+Cr)/Cit in prostatitis tissue has a histopathologic origin. The luminal space from which the majority of the MR-observed Cit signal originates [23,29], might become compressed as a result of the inflammatory process, thus resulting in semen content reduced, contributing to abnormal levels of Cit [30–32]. Meanwhile, the Cho level was not elevated significantly. Therefore the ratio of (Cho+Cr)/Cit of prostatitis was elevated for reduced Cit concentration. PCa tissue, however, had a higher mean ratio of (Cho+Cr)/Cit due to markedly elevated Cho concentration associated with marked reduction in Cit concentration [33].

In a study of 12 patients with chronic prostatitis in the PZ imaged at 1.5 T, Amita et al. [3], found that nine of the 12 patients with MRS data demonstrated elevated Cho levels and reduced or no Cit peak, findings that mimic those of PCa. Discrepancies might be related to individual variability and different standards of reference. In their study, step-section pathologic evaluation served as a standard of reference. Chronic prostatitis was defined by the presence of a dense inflammatory infiltrate composed of lymphocytes. In our present study, we used sextant biopsy as the reference standard. In addition, relative quantitative methods were used to study certain metabolite changes in our study. The normal contralateral PZ provide the reference values of the Cho height and of the Cit height on profile MRS for MRS measurements of the pathologic PZ. In the present study, the choline concentrations were not elevated in all cases with histopathologically confirmed prostatitis as this metabolic pattern was considered different from that of cancer.

Our study had several limitations. First, we evaluated lesions that originate in the unilateral PZ for a comparative study of MRS. Therefore, the bilateral PZ lesions or central zone lesions of the prostate were excluded. The second limitation of our study was the use of sextant biopsy for histologic confirmation, where a false negative is likely to occur. Patients with prostatitis without histologic confirmation had clinical and radiographic follow-up confirming prostatitis. However, the lack of histologic confirmation for these several cases of prostatitis and the relatively short-term follow-up available remains a limitation of this study. In addition, MRS was performed by pelvic-phase array coil, which there is a loss in signal-to-noise ratio (SNR) compared to endorectal coil [34]. Finally, a relatively small sample size and retrospective study design could have influences statistical analysis, and these results need to be confirmed prospectively with a large number of cases.

Conclusions

In summary, the ratio of (Cho+Cr)/Cit was not found to be suitable for the differentiation of prostatitis and PCa in the PZ; however, the metabolic pattern showed promise as an adjunct to conventional imaging in differentiating prostatitis from PCa in the PZ.

Conflict of interest

Authors declare no conflict of interest.

Ethical approval

The study was approved by ethics committees from all participating hospitals, and all patients provided signed informed consent forms before inclusion and before any MRI examinations.

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