

# Three-dimensional proton magnetic resonance spectroscopy and diffusion-weighted imaging in the differentiation of incidental prostate carcinoma from benign prostate hyperplasia

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**Abstract.** The present study evaluated three-dimensional proton magnetic resonance spectroscopy (MRS) and diffusion-weighted imaging (DWI) features in differentiating incidental prostate carcinoma (IPCa) and benign prostate hyperplasia (BPH) in the central gland of the prostate. The clinical and imaging data of 9 patients with IPCa, 118 patients with BPH [including those with glandular hyperplasia (GH), stromal hyperplasia (SH) and mixed hyperplasia (MH)], were retrospectively analyzed. The mean (choline + creatine)/citrate (CC/C) value of 3D MRS, the apparent diffusion coefficient (ADC) value and the minimal ADC value of DWI were compared between carcinoma and non-carcinoma tissues. The mean CC/C values were  $1.04 \pm 0.28$ , and  $1.09 \pm 0.58$  in IPCa and BPH, respectively ( $t = -0.205$ ,  $P = 0.838$ ). No significant difference in CC/C values ( $\chi^2 = 2.595$ ,  $P = 0.458$ ) could be detected between IPCa, GH, SH and MH groups. The ADC values of the central gland only differed between IPCa ( $1.48 \pm 0.18$ )  $\times 10^{-3}$  and GH ( $1.60 \pm 0.16$ )  $\times 10^{-3}$  mm<sup>2</sup>/sec ( $P = 0.037$ ). The minimal ADC values were similar between IPCa ( $1.15 \pm 0.10$ )  $\times 10^{-3}$  and BPH ( $1.14 \pm 0.11$ )  $\times 10^{-3}$  mm<sup>2</sup>/sec, no significant differences could be detected between IPCa and GH ( $P = 0.930$ ), IPCa and SH ( $P = 0.192$ ), and IPCa and MH ( $P = 0.544$ ). Although

the ADC values of the central gland of the prostate differed between IPCa and GH, the findings of the present study therefore indicate that combining 3D MRS with DWI cannot potentially improve the detection of IPCa.

## Introduction

Incidental prostate cancer (IPCa) is diagnosed incidentally from the histopathological examination of specimens obtained at the time of transurethral resection of the prostate (TURP) or adenectomy intended to treat benign prostatic hyperplasia (BPH). Although the majority of cases of IPCa are clinically insignificant, the biological behavior of IPCa may change, and the speed of progression of individuals remains unpredictable (1). Therefore, the accurate preoperative identification of IPCa is of great importance, as these patients would benefit the most from an appropriate treatment for IPCa.

Recently, multi-parametric magnetic resonance imaging (MRI) techniques, including T2-weighted imaging (T2WI), magnetic resonance spectroscopy (MRS) and diffusion-weighted MRI (DWI), are useful tools for the diagnosis of prostatic diseases, including the central gland (CG) and peripheral zone (PZ) of the prostate. The results of prior studies (2-12) indicate that the apparent diffusion coefficient (ADC) value of malignant regions was lower than that of the benign regions, and the [choline (Cho) + creatine (Cre)]/citrate (Cit) (CC/C) value of the former was higher than the latter.

There are a number of studies concerning the morphological and functional parameters of MRI on the CG and PZ of clinical prostate cancer (4-12); however, to the best of our knowledge, no public literature concerning MRS and DWI in IPCa in the CG of the prostate. The present study aimed to investigate the differences in conventional MRI manifestation, CC/C value, and ADC value between IPCa and BPH, and whether there are benefits to using these techniques to differentiate between the two diseases.

## Materials and methods

**Patients.** Informed consent was waived by the Nantong Medical Institutional Review Board for this retrospective study. All

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patients who underwent MRI of the prostate (T1WI, T2WI, MRS and DWI) between July 2006 and March 2013 in the radiological database of the Third People's Hospital of Nantong were retrospectively reviewed. In total, 164 patients who had been diagnosed as BPH on MRI then underwent TURP were collected.

A total of 9 patients were postoperatively diagnosed with IPCa, (mean age,  $73.56 \pm 5.18$  years; range, 66–84 years). Mean total-prostate specific antigen (T-PSA),  $10.87 \pm 4.80$  ng/ml; range, 5.19–20.97 ng/ml. Gleason scores (13) varied from 2 to 7, including lower scores (2 or 3 or 4) in 3 cases (33%) and higher certainty scores (5 or 6 or 7) in 6 of the 9 patients (67%) with IPCa. Among these 9 patients with MRI imaging, 7 exhibited MRS and 8 exhibited DWI.

A total of 155 patients were definitively diagnosed with BPH following surgery, of whom 118 underwent MRS or DWI before operations (mean age,  $69.38 \pm 6.43$  years; range, 55–87 years). Mean T-PSA  $14.39 \pm 11.51$  ng/ml, range 0.75–92.50 ng/ml. Preoperative MRS was performed in 99 patients, including 7 cases of glandular hyperplasia (GH), 30 cases of stromal hyperplasia (SH), 62 cases of mixed hyperplasia (MH). In total, 85 patients underwent preoperative DWI, which revealed that there were 7 cases of GH, 18 cases of SH and 63 cases of MH.

**MRI.** All MRIs were performed using GE 1.5 SignaTwinSpeed magnetic resonance scanner (GE Healthcare, Chicago, IL, USA).

**Conventional MR scan.** The patients were examined using a body coil for excitation and an abdominal phased array coil for reception. A fast spin-echo (FSE) T2WI was applied with the following parameters: Repetition time/echo time (TR/TE), 3,500/85 msec; echo train length (ETL), 19; slice thickness/gap 5/0.5 mm; field of view (FOV), 24x24 cm; number of excitations (NEX), 4; matrix, 320x256. The parameters of T1WI were as follows: TR/TE, 450/12 ms; slice thickness/gap, 5/0.5 mm, FOV 24x24 cm; NEX, 2; matrix, 256x192.

**3D  $^1\text{H}$ -MRS scan.** Before April 2008, patients were scanned using FSE T2WI with an endorectalcoil (TR/TE, 3,500/85 msec; ETL, 19; slice thickness/gap, 3/0 mm; FOV, 13x13 cm; NEX, 4; matrix, 320x256). These resulting images were used as a scanogram of 3D  $^1\text{H}$ -MRS examination and images were integrated with metabolic and anatomical information. A 3D  $^1\text{H}$ -MRS examination was performed using the prostate spectroscopy and imaging examination (PROSE) sequence (TR/TE, 1,000/130 msec; FOV, 11x11 cm; NEX, 1; matrix, 16x8; scanning time, 17–19 min). The axial images were used to guide the positioning of the spectroscopic volume of interest. This volume was selected to maximize coverage of prostate while minimizing the inclusion of periprostatic fat and rectal air. In the axial plane, the saturated zone was added on to the edge of the region of interest to eliminate the effects of fat tissues around the rectangular region of interest and endorectal gas at the rear of prostate. The conventional automatic pre-scan was performed prior to collection of MRS data, including automatic shimming and water suppression; full width half maximum was usually <15 Hz for collecting MRS data. After April 2008, patients were scanned using FSE

T2WI with a body coil line. 3D  $^1\text{H}$ -MRS examination was performed using PROSE sequence (TR/TE, 1,000/130 msec; FOV, 11x11 cm; NEX, 10; matrix, 12x8; total scan time, 16 min 4 sec).

**DWI scan.** A single-shot EPI sequence was used, with b values of 0 and 800 sec/mm<sup>2</sup>. Before February 2006, the body coil was used as the receiver coil (TR/TE 3,000/6.6 msec; slice thickness/gap, 6/0 mm; FOV, 26x26 cm; NEX, 2; matrix, 96x96; scan time, 24 sec). After February 2006, the abdominal phased array coil was used as the receiving coil (TR/TE, 3,500/56.4 msec; slice thickness/gap, 6/0 mm; FOV, 26x26 cm; NEX, 4; matrix, 128x128; scan time, 56 sec).

#### *Imaging analysis*

**MRS.** The criteria of usable MRS voxels was as follows: i) At least 75% of the voxel was located in the central gland, and had not been polluted by the signals from unsuppressed water and fat; ii) the urethra and periurethral glands were not included; and iii) the signal-to-noise ratio of three main metabolites, Cho, Cre and Cit, in each spectrum was >3.

**DWI.** ADC values in each slice of the central gland of each patient (the ADC values of the central gland) and minimal ADC value in the central glands (the minimal ADC values) were measured. The region of interest (ROI) placement guidelines for the central gland ADC values were as follows: The largest ROI of central gland in all scanning planes was hand-painted, the ROI edges were as far as possible consistent with the edges of the central gland. The ROI placement guidelines for the minimal ADC value were as follows: i) The ROI was placed in the central gland where the ADC value was lowest (referring to the ADC map); ii) the junction area of the peripheral zone, the central zone, the urethra, blood vessels, hemorrhage or calcification were avoided; and iii) ROI was oval with an area of 30–50 mm<sup>2</sup>.

**Statistical analysis.** All data were statistically analyzed using SPSS16.0 software (SPSS, Inc., Chicago, IL, USA). All data were expressed as mean  $\pm$  standard deviation. The group data were firstly tested to assess whether they were distributed normally. The independent-samples t-test was used to compare data between two groups. Levene's test was first used to compare between data among three groups, with the data that met the homogeneity of variance were compared using the  $\chi^2$  test of variance, the data which did not meet the homogeneity of variance were compared using the Kruskal-Wallis H-test.  $P < 0.05$  was considered to indicate a statistically significant difference.

## **Results**

**Manifestation of IPCa on conventional MRI and DWI**  
**Conventional MRI findings.** A total of 9 patients exhibited prostate enlargement to varying degrees, observed by T2WI, which was more evident in the central gland with mixed signal intensity, different numbers of hyperplastic nodules with hyperintensity or hypointensity were visible, the peripheral zone was compressed and thinned; 4 patients exhibited homogeneous hypointensity on T1WI imaging, 5 patients exhibited punctate hyperintensity within the hypointensity area, which were

Table I. CC/C, ADC values of the central gland and the minimal ADC values of IPCa and BPH (including GH, SH and MH).

Group	n	CC/C value	n	Central gland ADC value	Minimal ADC value
IPCa	7	1.04±0.28	8	1.48±0.18	1.15±0.10
BPH	99	1.09±0.58	88	1.49±0.14	1.14±0.11
GH	7	0.99±0.05	7	1.60±0.16	1.21±0.12
SH	30	1.31±0.94	18	1.37±0.10	1.15±0.06
MH	62	0.99±0.31	63	1.48±0.12	1.12±0.10

CC/C, (choline + creatine)/citrate; ADC, apparent diffusion coefficient; IPCa, incidental prostate carcinoma; BPH, benign prostate hyperplasia; GH, glandular hyperplasia; SH, stromal hyperplasia; MH, mixed hyperplasia. ADC unit,  $\times 10^{-3} \text{ mm}^2/\text{sec}$ .

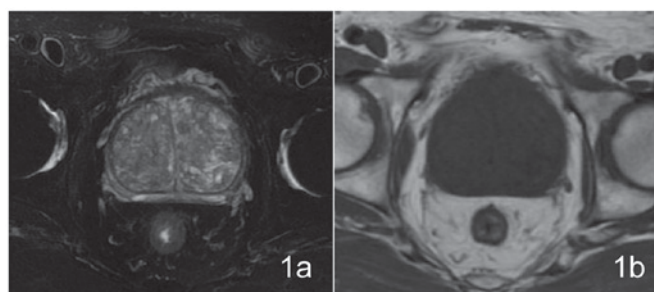


Figure 1. A 76-year-old man with incidental prostate carcinoma. (A) The central gland displayed mixed signal intensity on T2WI. (B) The center gland exhibited homogeneous hypointensity on T1WI. T2WI, T2-weighted imaging.

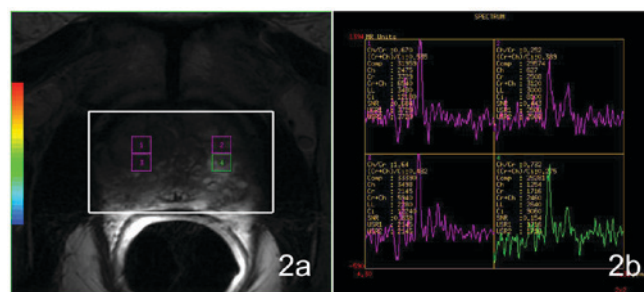


Figure 2. A 76-year-old man with incidental prostate carcinoma. (A) The voxels and (B) corresponding MRS map, the CC/C values of the four voxels were 0.535, 0.389, 0.482 and 0.275, respectively.

considered to be due to bleeding (Fig. 1). The pelvis and vertebral body exhibited no abnormal signal within the scan range and no lymph node enlargement was observed in the pelvic or groin areas. Patients were all diagnosed as BPH preoperatively by MRI. IPCa did not exhibit areas of clear high signal intensity on DWI.

**Analysis of 3DMRS and DWI Data.** Results of 3DMRS and DWI are depicted in Table I.

**CC/C values.** There was no significant difference ( $t=-0.205$ ,  $P=0.838$ ) between CC/C values of the IPCa and BPH groups. No significant difference ( $\chi^2=2.595$ ,  $P=0.458$ ) could be detected among the IPCa, GH, SH and MH groups (Fig. 2).

**ADC values of the central glands.** There was no significant difference ( $t=-0.224$ ,  $P=0.823$ ) between the two groups of IPCa and BPH. There was a statistically significant ( $F=6.181$ ,  $P=0.001$ ) difference between the IPCa, GH, SH and MH groups. Of the four groups, the difference was statistically significant between the IPCa and the GH ( $P=0.037$ ), in comparison of the IPCa and SH ( $P=0.127$ ), IPCa and MH ( $P=0.908$ ), no significant differences could be detected (Fig. 3).

**Minimal ADC values.** No statistically significant difference existed between the IPCa and BPH groups ( $t=0.139$ ,  $P=0.890$ ). The difference in the minimal ADC values among the four groups was statistically significant ( $F=2.897$ ,  $P=0.039$ ). No significant differences could be detected between IPCa and GH ( $P=0.930$ ), IPCa and SH ( $P=0.192$ ), and IPCa and MH ( $P=0.544$ ) (Fig. 4).

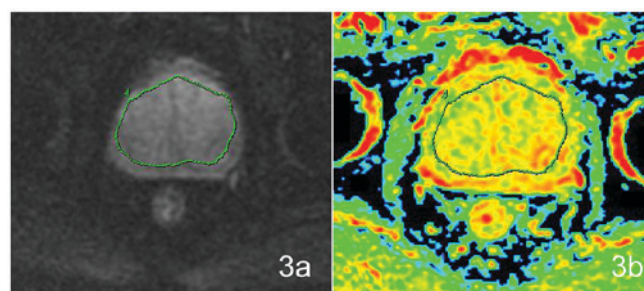


Figure 3. A 76-year-old man with incidental prostate carcinoma. (A) ROI of the ADC value of the central gland and (B) corresponding ADC map, the ADC value was  $1.59 \times 10^{-3} \text{ mm}^2/\text{sec}$ . ADC, apparent diffusion coefficient.

## Discussion

As the non-invasive functional MRI, MRS and DWI techniques are not influenced by the experience of the operator and are conducive to improving the diagnostic efficacy (14-18), and serve an important role in the detection, localization, and staging of prostate cancer (9).

IPCa refers to that patients have been clinically diagnosed with BPH, with no evidence of prostate cancer upon digital rectal examination or various imaging examinations. After undergoing open prostatectomy or TURP, the prostate cancer tissues were found in the inspection samples. There was a remarkable difference in morbidity between domestic and abroad reports (19-22). In this study, out of 164 patients who were diagnosed as BPH by MR examination after TURP, 155 patients were confirmed as BPH, 9 patients were confirmed



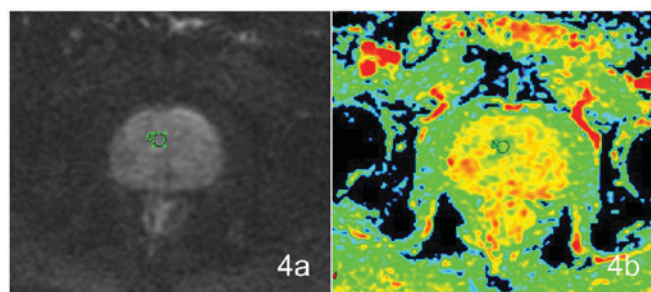


Figure 4. A 76-year-old man with incidental prostate carcinoma. (A) Region of interest of the minimal ADC value and (B) corresponding ADC map, the ADC value was  $1.30 \times 10^{-3} \text{ mm}^2/\text{sec}$ . ADC, apparent diffusion coefficient.

as IPCa, accounting for 5.49%. The group of 9 patients with IPCa had the following characteristics: i) PSA levels were increased slightly compared with those with BPH; and ii) tumors had low Gleason scores and they were mostly well- or moderately differentiated carcinomas.

Cancer in the CG of the prostate exhibits the following features: Homogeneous low signal intensity on T2WI, lack of capsule, ill-defined margins, increased CC/C value, high signal intensity on DWI and decreased ADC value (2,3,8,12,23). In the present study, the T1WI and T2WI findings for the 9 patients with IPCa were similar to those with BPH, and did not exhibit any apparently cancerous areas. As such, they were all preoperatively diagnosed as BPH by MRI.

The CC/C value of IPCa and BPH was not significantly different in the present study. Furthermore, no significant difference in either the ADC value of the central gland or the minimal ADC value were identified. According to the pathological findings, the BPH group was divided into 3 subgroups: GH, SH and MH. Compared with IPCa, the differences in CC/C values were not statistically significant, and the IPCa CC/C value was lower than that of SH, and slightly higher than those of GH and MH; the CC/C value of IPCa was between those of BPH groups. There was only statistically significant difference in ADC value, which was between IPCa and GH; there were no statistically significant differences in minimal ADC value between IPCa and various BPH groups. It was therefore clear that the CC/C value and the ADC value of IPCa were close to those of BPH groups, which indicated at the difficulties of preoperative MRI diagnosis.

Previous studies reported that the CC/C and ADC values of benign prostate disease were significantly different from those of prostate cancer (3,24-27). As only the proportion of glandular and stromal tissue was changed in BPH, which would not have a significant impact on the secretory function of the gland, These pathological features were different from clinically detected prostate cancer. In addition, Montironi *et al* reported that the staging, positive surgical margin rate, Gleason score and invasiveness of IPCa were lower than those of the clinically detected prostate cancer (28,29), which indicated that IPCa is less aggressive compared with clinically detected cancer.

According to a previous study (3), GH exhibited hyperintensity on T2WI, with pathology revealing that it contained a large number of dilated glandular ducts and retention cysts and fewer stromal components. SH exhibited hypointensity, with pathology revealing that the hyperplastic nodules contained

more collagen and stromal cells (including fibroblasts and smooth muscle cells) and fewer glandular components (3). The ADC value of the prostate gland tissue was higher than that of the prostate stromal tissue (30). Notably, the pathological findings of the present study revealed the presence of 7 cases of GH, 18 cases of SH and 63 cases of MH, all displayed asymmetrical enlargement of central glands with heterogeneous nodules on T2WI. On the ADC images, 4 cases (4/7) of GH had hyperintensity, 12 cases (12/18) of SH exhibited considerable hypointensity, measured using two methods of the central gland ADC values and the minimal ADC value. SH is formed of a greater cellular component, is more dense and contains less extracellular fluid than GH; these differences could explain the smaller ADCs in SH, in accordance with the findings of a previous study (3).

In addition, a prior report indicated that metabolic performance of SH could be similar to that of atypical prostate cancer (31); the results of a present study were similar. The CC/C value of the SH group was the highest of the four groups assessed in the current study. In the preoperative MRI diagnosis, the CC/C values for certain SH cases were significantly increased, reaching a maximal value of 8, providing evidence of the metabolic characteristics of typical prostate cancer, and leading to 5 cases being misdiagnosed as cancer. This misdiagnosis may be due to the fact that SH tissues have less glandular and ductal components, and low Citelevels, meaning that the CC/C value was increased.

There are limitations to the present study. First, because it is a retrospective study, there may be selection bias in the patient cohort. Second, the IPCa sample size was relatively small. Since the exact location of the occurrence of the incidental carcinoma could not be obtained by pathological examination following TURP, the CC/C values of all available voxels in the central gland were measured in the present study. Owing to the impact of the partial volume effect in sample slices, the measured CC/C values may have been slightly lower than those of the areas of cancer, although they could also reflect metabolic changes to IPCa. In addition, two methods were used to measure ADC values in the present study: The ADC value of the central gland and the minimal ADC value of the central gland. The two methods had advantages and disadvantages. Measuring the ADC value of the central gland, the ROI was drawn as large as possible, in accordance with the size of the central gland. The measured value was the ADC value of the central gland at this slice, including the cancerous and non-cancerous areas, and even calcification and bleeding within the ROI. Owing to the impact of the partial volume effect, measurement of the ADC value of the central gland could not reflect the real ADC value of the cancerous area, although use of this method was suitable when the lesion location could not be defined. The second method was to measure the minimal ADC value of the central gland, which avoided the partial volume effect (5,9-11,17,18). The minimal ADC value of the cancerous tissue was lower than that of the normal tissue or benign lesion, which may reflect a more realistic ADC value.

Taken together, the results of the present study demonstrate that the performance characteristics of IPCa are similar to those of BPH on 3D MRS and DWI, meaning that IPCa cannot be distinguished preoperatively from

BPH using current MRI examination techniques. Further and larger studies are required, however, to confirm these findings.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contribution

JL and QZ guaranteed the integrity of the study. XQZ, XRY and JL were involved in study conception and design. ZLD and XFM conducted the clinical studies and data analysis. XQZ and XRY were involved in manuscript preparation. QZ performed statistical analysis and edited the manuscript.

### Ethics approval and consent to participate

Informed consent was waived by the Nantong Medical Institutional Review Board for this retrospective study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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