Added value of MR spectroscopy to combined T2-weighted and diffusion weighted MRI in prostatic lesions characterization

Nahla Mohamed Ali Hasan[a*], Mohamad Hasan Alam-Eldeen[a], Mohamed Abdelghany Elsherif[a], Mohammed Hazem[a,b]

[a]Diagnostic Radiology Department, Faculty of Medicine, Sohag University, Sohag, Egypt. [b]Surgery Department, College of medicine, King Faisal University, P.O.Box:400,Al-Ahsa 31982, Saudi Arabia.

Abstract

Background: Recently, multiparametric magnetic resonance imaging has been extensively used for early detection and localization of clinically significant prostate cancer. Magnetic resonance spectroscopy provides chemical information about metabolites in normal and abnormal tissues. It isn't widely used in routine imaging of prostatic lesions.

Objectives: to evaluate the diagnostic benefit from adding MRS to combined T2WI and DWI (bi-parametric MRI) in prostatic lesions diagnosis.

Patients and Methods: This prospective study included MRI prostate of 128 adult male obtained by using 1.5 Tesla machine. They were presented by clinically suspected prostatic lesions and elevated PSA level (> 4 ng/dl). MRI protocol included T1WI, T2WI, DWI and MRS. Diagnostic accuracy of bi-parametric MRI was compared with that of MRS alone and that after adding MRS to T2WI and DWI using the histopathological diagnosis as the standard of reference.

Results: 68 (53%) patients were histopathologically diagnosed with malignant prostatic lesions and 60 (47%) patients with benign lesions. Combined MRS with bi-parametric MRI had the highest diagnostic accuracy of 96.8% with sensitivity, specificity, PPV, and NPV of 100%, 93.3%, 94.4%, and 100% respectively compared with those of bi-parametric MRI; 71.9 % accuracy, 76.5% sensitivity, 66.7 % specificity, 72.2% PPV and 71.4% NPV and MRS that had 90.6 % accuracy, 100% sensitivity, 80 % specificity, 85% PPV and 100% NPV.

Conclusion: Adding MRS to T2WI and DWI is a promising diagnostic tool for better detection and characterization of different malignant and benign prostatic lesions compared to bi-parametric MRI.

Key words: bpMRI, mpMRI, MR spectroscopy, Prostate cancer.

DOI: 10.21608/svuijm.2022.135321.1302

***Correspondence**: **nahla.hasan@ymail.com**

Received: 22 April,2022.

Revised: 8 May,2022.

Accepted: 10 May, 2022.

Cite this article as: Nahla Mohamed Ali Hasan, Mohamad Hasan Alam-Eldeen, Mohamed Abdelghany Elsherif, Mohammed Hazem. (2022). Added value of MR spectroscopy to combined T2-weighted and diffusion weighted MRI in prostatic lesions characterization. *SVU-International Journal of Medical Sciences*. Vol.5, Issue 2, pp: 237-252.

Copyright: © Hasan et al. (2022) Immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge. Users have the right to Read, download, copy, distribute, print or share link to the full texts under a Creative Commons BY-NC-SA 4.0 International License.

Introduction

Diseases primarily affecting prostate gland are inflammation, benign nodular enlargement, and tumors **(Epstein , 2010).**Prostate cancer (PC) is the second most common diagnosed cancer and the sixth leading cause of cancer death in men worldwide **(Cancer Today, 2020).**Early detection of PC has a better chance for successful treatment. However, PC detection and differentiation from benign entities as early as possible is still challenging **(Jemal et al, 2010)**.

The currently used clinical screening tools for PC diagnosis including prostate specific antigen (PSA) test and transrectal ultrasound (TRUS) guided biopsy are lacking sensitivity and specificity. Recently multi-parametric MRI (mpMRI) prostate that combines anatomic T2WI with functional sequences has emerged as a very useful tool for PC diagnosis estimating a high accuracy**(Barrett and Haider, 2017)**. According to the updated version (PI-RADS v2.1), mpMRI protocol for prostate imaging consists of T2-weighted imaging, DWI, and DCE-MRI**(PI-RADS2019)**. The role of DCE is limited, though considered an essential component of the mpMRI prostate examination. Despite of several studies reported a significant role of PI-RADS Version 2.1 in PC diagnosis; A wide variety of normal and abnormal entities mimic PC at Mp-MRI causing diagnostic challenges, such as chronic prostatitis; granulomatous prostatitis; hypertrophic nodule; focal changes related to previous exposure to radiation and normal displaced central zone**(Yu et al. 2014)**.

MR spectroscopic imaging has the ability to provide chemical information about metabolites in normal and abnormal tissues. Elevation of choline (Cho) levels and reduction of citrate (Cit) have been observed in cancerous tissue relative to benign prostatic tissue. The ratio of choline+creatine/citrate (Cho+Cr)/Cit has been used as a routine evaluation system **(Barentsz et al., 2012)**. For example, a higher ratio of (Cho+Cr)/Cit is found in cancer tissue than in benign prostatic hyperplasia **(Li et al., 2007)**, however its role in differentiating prostatitis is controversial **(Zhang et al., 2017 ; Sah et al., 2015).**

MRS is not widely used in routine clinical practice but used in research studies and academic centers primarily due to its low availability, high costs and unclear clinical benefit**(Stabile et al., 2020)**. In this study, we aimed to evaluate the diagnostic benefit from adding MRS to combined T2WI and DWI (bi-parametric MRI) in detection and characterization of different prostatic lesions.

Patients and Methods

- ***Study design***

This prospective study took place during the period from September 2019 to December 2021. After obtaining the Ethical approval from our intuitional review board (IRB) and all patients gave their informed written consent. All techniques used in this study were performed in accordance with the Helsinki declaration 1975, as revised in 2013. Initially, the study included 143 consecutive patients presented clinically with suspected prostatic lesions and elevated PSA level (> 4 ng/dl) referred for MRI

examination from relevant outpatient clinics. Exclusion criteria included patients with past history of prostate surgery or received any treatment such as endocrine therapy, brachytherapy, radiotherapy, etc., or underwent TRUS biopsy before MRI examination. 15 patients had prostatic cysts and abscesses were excluded because these lesions are very rarely mimic cancer prostate on mp-MRI or cause diagnostic dilemma, so finally 128 cases were included in this study. Final diagnoses depended on the histopathological results as the slandered of reference.

- ***MRI Technique***

All MRI examinations had been obtained by using 1.5 Tesla machine (Philips-Acheiva), Netherlands. The patients were examined in supine position without prior bowel preparation. Pelvic phased array coil was used for all patients and was combined with the endo-rectal coil for 8 patients, where their simultaneous use provides excellent signal to noise ratio, however the endo-rectal coil is time consuming, and uncomfortable for the patients.

Pulse sequences included sagittal, coronal and axial breath-hold fast spine echo T2-weighted images, Axial T1WI VIBE, and DWI which was obtained at multipoint b value (0, 100, 800, 1000, 1500 s/mm with main region of interest 45 mm^2). On the workstation ADC maps were reconstructed and mean ADC value was calculated.

MRS was performed for all patients to evaluate the total prostatic volume aligned to axial T2WIsin the same session. It was performed using 3D-chemical shift imaging protocol. Multiple external saturation bands were used to avoid field non-homogeneity and magnetic susceptibility associated with periprostatic fat, bone and urine within urinary bladder. Metabolite concentrations of citrate, creatine and choline compounds were estimated and (Cho+Cr)/Cit ratio was calculated in peripheral and transition zones (quantitative assessment) as well as visual comparison of the peak heights of citrate and choline (qualitative assessment). Data acquisition parameters are listed in **(Table 1**).

Table 1. mpMRI acquisition parameters.

Sequences	TR	TE	FOV (mm)	Slice thickness (mm)	Intersection gap (mm)	Matrix	Acquisition time
T2WI Sagittal	3030	98	200 X 200	4	0.8	320X256	3 min
T2WI Coronal	3000	98	200 X 200	4	0.4	320X256	4 min
T2WI Axial	4840	84	200 X 200	3	0.8	320X256	4.2 min
Axial T1WI VIBE	7.23	2.5 5	250 X 250	3	0.8	192X192	20 sec
DWI	8000	80	220 X 220	5	0	14X140w	4 min
MRS	1000	130	240 X 240	**Voxel volume:1 cm^3**	-	-	15 min

- ***Image analysis***

All MRI findings were assessed separately by two radiologists with 10 and 7 years of experience in urogenital radiology.

First interpretation session: for combined T2WI and DWI (bi-parametric MRI). The following data were recorded for any prostatic lesion; site, size, morphology, signal intensity (T1WI, T2WI, DWI and ADC map) and ADC value as well as presence or absence of extra-prostatic extension.

Based on PI-RADS version 2.1 Assessment Categories; PI-RADS 1 – Very low, PI-RADS 2 – Low, PI-RADS 3 – Intermediate, PI-RADS 4 – High, PI-RADS 5 – Very high. In absence of DCE-MRI, Scoring was based on T2WI for the transition zone(TZ) lesions while DWI was used for the peripheral zone (PZ) lesions with category 3 lesions remained as category 3 and not upgraded.

For transition zone lesions, round shape lesion with well-defined margins and visible capsule favors a diagnosis of BPH nodules. Prostatic infarction was diagnosed as low T2 signal, not restricted on DWI, while prostatic atrophy was suspected when abnormally low signal intensity T2 was associated with tissue volume loss, however corresponding diffusion restriction is challenging. Prostatitis was difficult to be suspected as it is one of the most important mimics to PC on bpMRI.

For multifocal lesions, index lesion was used for statistical analysis according to PI-RADS version 2.1 definition; the index lesion is defined as the lesion that shows the highest PI-RADS assessment category. If the highest PI-RADS assessment category is specified to more than or equal two lesions, the index lesion is that revealed extraprostatic extension. If extraprostatic extension was not present in any of the detected lesions, the index lesion was the lesion that showed the largest dimensions and the highest PI-RADS assessment category. Bi-parametric MRI (bpMRI) diagnosis was reported considering PI-RADS 1 & 2 as benign tissue, while PI-RADS 3 &4 & 5 as malignant tissue.

Second interpretation session: for MRS. According to ESUR prostate MR guideline of quantitative MRS for 1.5 T. references (**Barentsz et al., 2012**); PI-RADS 1 (definitely benign tissue), PI-RADS 2 (probably benign tissue), PI-RADS 3 (possible malignant tissue), PI-RADS 4 (probably malignant tissue) and PI-RADS 5 (definitely malignant tissue). For peripheral zone lesions, we used ratio > 0.58 suggesting PC while < 0.44 indicates benign tissue. For central zone lesions, ratio > 0.66 suggesting PC and < 0.52 for benign tissue were used. MRS diagnosis was reported considering PI-RADS 1 & 2 as benign tissue, while PI-RADS 3 & 4 & 5 as malignant tissue.

Third interpretation session: for MRS combined to the bpMRI. Final mpMRI diagnosis of the prostatic lesions was reported.

- ***Prostatic biopsy guided by transrectal ultrasound***

After MRI study, all patients were subjected to TRUS using Toshiba Aplio 500 device with a high frequency transrectal probe (8-10 MHz) and the patient in lithotomy position. After introduction of the lubricated probe into the rectum and prostate gland was

visualized, longitudinal and transverse images were obtained, the prostate volume was assessed and any focal abnormality site and size was detected. TRUS guided prostatic biopsy usingthe standard 12-core biopsy scheme was done under local anesthesia.

Open prostatectomy was performed for cases with positive TRUS-guided biopsy for PC, and the diagnosis of prostatic cancer was confirmed.

Final diagnosis: It depended upon the histopathology result. According to PI-RADS v2.1, PC was diagnosed if the lesion had any of the followings; Gleason score ≥7 (including 3 + 4 with prominent but not predominant Gleason 4 component), volume >0.5cc, and extraprostatic extension.

Statistical analysis

Descriptive analyses of the demographic, clinical, radiological, and pathological characteristics were performed by using the SPSS program (version 21). The quantitative variables were described with mean ± standard deviation and range, while qualitative variables were represented with numbers and percentages. T-student test was applied to test the presence of significant differences between two independent comparable quantitative variables and Chi square was applied to test the presence of significant differences between two independent comparable qualitative variables (benign versus malignant), depending on the features assessed. The P-value < 0.05 was considered statistically significant.

The diagnostic performance was assessed. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy as well as their 95% confidence interval of bi-parametric MRI (T2W imaging and DWI), those of MRS alone and those of combined MRS to the bi-parametric MRI using the histopathological diagnosis as a standard of reference.

Cohen's kappa test was used for calculation of interobserver variability considering 1% –2% slight agreement, 21% –40% fair agreement, 41% –60% moderate agreement, 61% –80% substantial agreement and 81% – 100% almost perfect or perfect agreement.

Results

Patients

In this study, we enrolled 128 patients whose age range was between 43 and 80 years old (mean 62.9 ± 12.2). The mean PSA level was significantly higher for PC than for benign lesions (*p* value <0.001), **(Table 2).**

Histopathological findings

In descending order of frequency, the histopathologicaldiagnoses of the included 128 lesions were 68 prostate cancer, 25 BPH, 15 granulomatous prostatitis, 12 prostatic atrophy, and 8 prostatic infarction.

The malignant prostatic lesions were classified into 60 cases of prostatic adenocarcinoma with Gleason score 3+4 for 7 (12%) cases, 4+3 for 15 (25%) cases, 4+4 for 18 (30%) cases and 4+5 for 20 (33%) cases while 8 cases were prostatic sarcoma, **(Table 2).**

Table 2 . Age, PSA level and histopathology of the studied patients

Parameter	Benign prostatic lesions	Malignant prostatic lesions
Age mean (range)	60.9 ± 0.45 (43-77)	57.1 ± 0.36 (48-80)
PSA mean (range)	5.8 ±0.14 (4 - 12 ng/dl)	61.4±0.34(23-103 ng/dl)
Histopathology: no. (%)	BPH: 25 (42%) Granulomatous prostatitis: 15 (25%) Prostatic atrophy:12 (20%) Prostatic infarction: 8 (13%)	PZ adenocarcinoma: 52 (76%) TZ adenocarcinoma : 8 (12%) Prostatic sarcoma: 8(12%)
Total	60	68

bpMRI assessment results

As regard the 68 lesions of PC, according to PI-RADS version 2.1[5], bpMRI correctly diagnosed 52 (76.5%) lesions showed low T2 signal and restricted diffusion with mean ADC value of 1.02 ± 0.22 x 10^{-3} mm^2/s. 48 lesions were PI-RADS 4 &5 while the remaining 4 lesions were PI-RADS 3, 44 lesions were peripheral zone carcinoma and 8 lesions had prostate sarcoma involving both peripheral and transition zones. However, bpMRI showed false negative results in 16 (23.5%) lesions; 8 of them were proved as transition zone carcinoma (bpMRI diagnoses were BPH) and 8 lesions showed focal peripheral zone asymmetry of isointense T2 signal to normal prostatic tissue and did not show diffusion restriction.

On the other hand, from the 60 benign lesions; 40 (66.7%) lesions were correctly diagnosed by the bpMRI of PI-RADS 1 & 2 (25 BPH, 8 prostatic infarctions and 7 chronic prostatitis) with the mean ADC value for BPH was 1.51 ± 0.11 x 10^{-3} mm^2/s, for chronic prostatitis was 1.48 ± 0.02 x 10^{-3} and for prostatic infarctions was 1.37± 0.09 x 10^{-3} mm^2/s, While the remaining 20 (33.3%) lesions (12 prostatic atrophy and 8 granulomatous prostatitis) had low signal on T2WI and showed diffusion restriction, they were reported as PI-RADS 3 & 4 and was considered as PC,**(Table 3).** Bi-parametric MRI had 76.5% sensitivity, 66.7% specificity, 72.2% PPV, 71.4% NPV and 71.9 % accuracy.

MR Spectroscopy assessment findings

According to PI-RADS scoring system of European Society of Urogenital Radiology (ESUR)prostate MR guidelines for quantitative evaluation of MRS **(Barentsz et al., 2012)**, MRS correctly diagnosed all 68 (100%) lesions of PC as PI-RADS 4 & 5 and 48 (80%) of benign lesions as PI-RADS 1 & 2, while the remaining 12 (20%) lesions were reported as PI-RADS 3 (4 cases were histopathologically diagnosed as granulomatous prostatitis and 8 cases were prostatic infarction with still significantly lower Cho+Cr/Cit ratio compared with those of PC), **(Table 3).**

Table 3. PI-RADS score of the prostate lesions on bpMRI, MRS and mpMRI

Pathology	bpMRP (T2+DWI)		MRS		mpMRI(T2+DWI+MRS)	
	PI-RADS score		PI-RADS score		PI-RADS score	
	1 , 2	3, 4, 5	1, 2	3, 4, 5	1, 2	3, 4, 5
Benign lesions (no.= 60)	40	20	48	12	56	4
Malignant lesions (no.= 68)	16	52	0	68	0	68

The mean of Cho+Cr/Cit ratio of PC (1.3 ± 0.51,ranged from 0.88 to 2.9) was significantly higher than that of benign lesions (0.53 ± 0.44 ranged from 0.33 to 0.78) (p-value < 0.05). MRS had 100% sensitivity, 80% specificity, 85% PPV, 100% NPV and 90.6 % accuracy.

Combined MR Spectroscopy and bpMRI assessment findings

Combined MRS with bpMRI (mpMRI) correctly diagnosed all 68 (100%) lesions of PC of BIRADS 5 and correctly diagnosed 56 (93.3%) of benign lesions of BIRADS 1&2 while 4 (6.7%) lesions of BIRADS 3, **(Table 3).**

mpMRI sensitivity, specificity, PPV, NPV and accuracy of mpMRI was 100%, 93.3%, 94.4%, 100% and 96.8% respectively, higher than those of bpMRI and those of MRS alone , **(Table 4).** The interobserver variability was 91.1% (almost perfect agreement).

Table 4: Comparison between the diagnostic accuracy of bpMRI, MRS and mpMRI for prostatic lesions.

Parameter	T2WI + DWI	MRS	T2WI + DWI + MRS
Sensitivity (%) (95% CI)	76.5% (64.6 - 86)	100% (94.7 - 100)	100% (94.7- 100)
Specificity (%) (95% CI)	66.7% (53.3– 78.3)	80% (67.7– 89.2)	93.3% (83.8– 98.2)
PPV (%) (95% CI)	72.2% (64–79.2)	85% (77.4– 90.4)	94.4% (86.8 -97.8)
NPV(%) (95% CI)	71.4% (61 - 80)	100% (93 to 100)	100% (94 - 100)
Accuracy (%) (95% CI)	71.9 (63.2–79.5)	90.6% (84.2- 95.1)	96.8% (92.2– 99.1)

Discussion

Based on the recent ESUR prostate MR guideline for PC diagnosis using Cho+Cr/Cit ratio cut-off points for both PZ and TZ to differentiate benign from malignant prostatic tissue**(Barentsz et al., 2012)**, our results allowed us to say MRS improved the diagnostic accuracy of prostatic MR imaging. We found the highest

MRI diagnostic accuracy of prostatic lesions was that of mpMRI (MRS combined to T2- and DWI) with sensitivity, specificity, PPV, NPV and accuracy of 100%, 93.3%, 94.4%, 100% and 96.8% respectively compared to those of bpMRI; and those of MRS alone. The diagnostic strength of the MRS was in its 100% sensitivity, thus no cases of PC were missed and its 100% negative predictive value, so PC could be excluded and unnecessary biopsy could be avoided.

Many researches in the last decade have studied the diagnostic accuracy of MRS in prostatic lesions assessment either solely **(Petrillo et al., 2014; Panebianco et al., 2010; Bhatia et al., 2007; Cirillo et al., 2008; Wetter et al., 2005; Sciarra et al., 2010)** or in different combinations with other functional and anatomic MRI procedures. Most of them combined MRS with T2WI (**Bhatia et al., 2007; Cirillo et al., 2008; Wetter et al., 2005; Destefanis et al., 2009),** some combined with DCE-MRI **(Panebianco et al., 2010; Sciarra et al., 2010; Sciarra et al., 2008)** and few studies combined MRS with T2WI and DWI **(Jagannathan and ., 2017)**.

In our study, the mean of Cho+Cr/Cit ratio of PC was significantly higher than that of benign lesions (p-value < 0.05), in accordance with the results reported by **(Shukla-Dave et al., 2007; Lahoti et al2017)**, (**Fig. 1 and 2).**

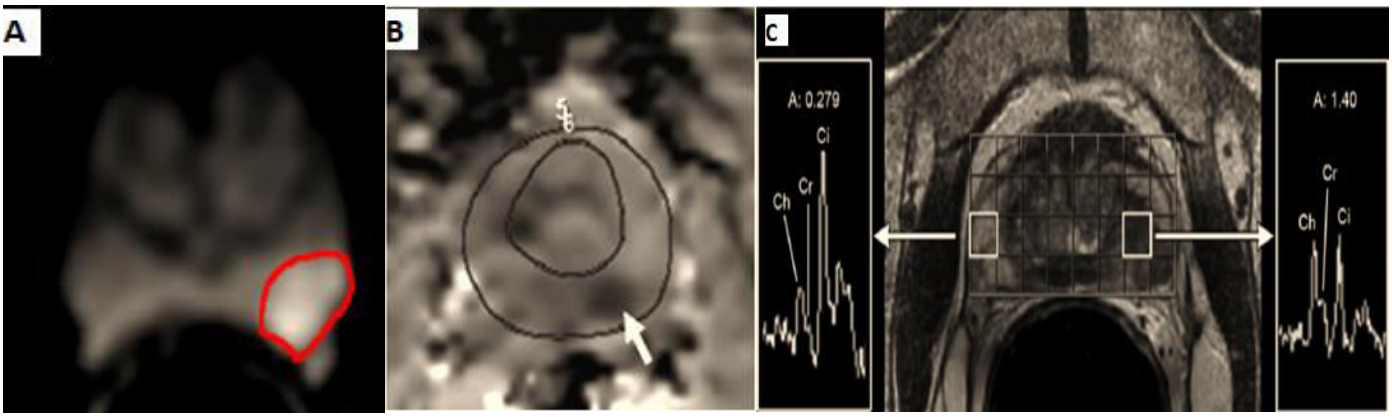

Fig. 1. 54 years old male patient with left PZ prostate adenocarcinoma: Left PZ focal restricted lesion highlighted in red at DWI (A) and of low signal on ADC map (arrow) with the whole prostate and central gland are outlined, ADC value; $\pm$1.3 x 10^{-3} mm^2/s (B). MRS (C) curve and values show malignant spectral pattern of the left PZ histologically proved prostatic carcinoma (increased choline level and reduced citrate level with increasedCho + Cr/Ci ratio (1.4) compared with the right PZ typical spectrum of non-cancerous tissue of high citrate peak Cho + Cr/Cit ratio (0.28).

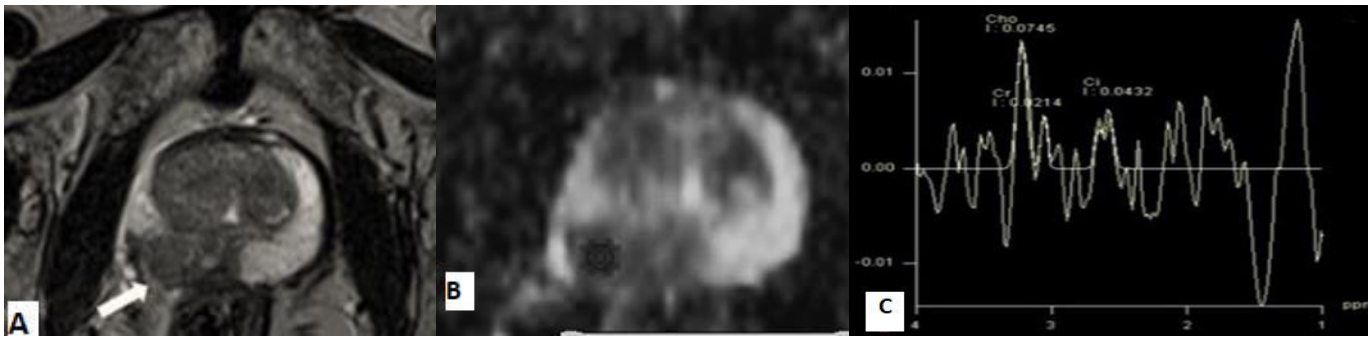

Fig. 2. 53 years old male patient with right PZ prostate adenocarcinoma:(A) Axial T2WI shows focal well-defined area of moderate hypo intensity in right PZcausing bulging and irregularity of capsule (arrow).(B) ADC map: The corresponding area showing restricted diffusion, of hypointense signal with ADC value $\pm$1.0 x 10^{-3} mm^2/s(C) MRS of the lesion shows elevated choline peak and reduced citrate peak increased Cho + Cr/Cit ratio(2.2).

Several previous literatures have shown improvement in PC diagnostic accuracy by adding MRS to MRI with some discrepancies in their results. **Fusco et al., 2017,** in their systematic data analyses of 33 studies from 2000 to 2016 on mp-MRI in PC detection, they reported Sensitivity and specificity values for T2-MRI of 75% and 60%, for MRS of 89% and 69%, and for combined T2-MRI and MRS of 79% and 57% respectively. They didn't found studies reporting the accuracy of MRS combined with DWI with or without T2WI combination.

In one of the few studies that reported the diagnostic accuracy of combined T2 & DWI and MRS included 26 patients with prostatic lesions, **Jagannathan and Indiran , 2017,**used Cho+Cr/Ci ratios > 0.75 for PC diagnosis, irrespective to its PZ or TZ location and accordingly they found the sensitivity, specificity, PPV, NPV and accuracy for combined T2 & DWI and MRS were 94.7, 42.9, 81.8, 75 and 80.8 higher than those of MRS; 84.2, 28.6, 76.2, 40, and 69.2 and respectively. **Bhatia et al., 2007**in their study found the combined MRI/MRS for detection of PC had the highest diagnostic accuracy with 100% sensitivity and 100% NPV similar to obtained in this study but had lower specificity, PPV and accuracy of 84%, 40%, and 86% respectively. As well, they reported a lower diagnostic accuracy of MRS than ours (80%, 85%, 21%, 99% and 85% of sensitivity, specificity, PPV, NPV and accuracy, respectively). **Petrillo et al., 2014,** in another study included 136 patients with PSA values ≤10 ng/ml. and by using Cho+Cr/Ci ratio threshold of 0.86 for PC diagnosis, MRI score (mMRI, DWI, and MRS) showed the highest sensitivity (0.84%) and negative predictive value (0.93%).

The higher MRS diagnostic accuracy values obtained in our study compared with those reported in most previous similar literatures could be explained by the different combinations of MRI techniques used; as we used MRS combined with T2

and DWI, while most others used MRS with T2 MRI only. Secondly the difference in Cho+Cr/Cit ratio cut-off threshold used in detection and characterization of prostatic lesions as we used two different ratios for PZ and TZ, while most previous studies used one threshold for PC diagnosis irrespective to its PZ or CZ location with a wide range of variations (from > 0.6 to > 0.86) (**Fusco et al.,2017**). For example (**Wang et al., 2008**)in their meta-analysis study for PC MRS diagnostic accuracy; they used two cut-off thresholds 0.75 and 0.86, for differentiating benign from malignant prostatic tissue. For 0.75 cut-off point, sensitivity, specificity, and corresponding 95% CI were 0.82, 0.68, and 83.4% respectively, while 0.86% cut-off point had sensitivity, specificity, and corresponding 95% CI of 0.64, 0.86 and 82.7% respectively. The last influential factor could be the multi-voxel MRS spectral analysis used in the current study aiming to evaluate total volume of the prostate, while up to our knowledge, most of other literatures MR spectral analysis was confined to the regions of T2 MRI abnormal low signal.

On another front, a multicenter study **(Weinreb et al., 2009)** found no incremental value of MRS over MRI for men with relatively low-volume and low-risk disease who underwent radical prostatectomy. However, MRS is a good diagnostic tool for aggressive cancers detection **(Villeirs et al., 2011)**.

The variable signal intensity of PC on T2WI is considered one of the most important challenging characteristics of PC MRI. Despite of most PCs in PZ or TZ have low signal on T2WI and restricted on DWI, PC can be presented only by focal glandular asymmetry without abnormal T2 signal or diffusion restriction. In addition, benign pathologies like granulomatous prostatitis, prostatic infarction and hyperplastic BPH nodules have similar T2 and DWI characteristics (**Yu et al., 2014 ; Kitzing et al., 2016**).

We found that using MRS as additional functioning technique could overcomes these dilemmas and improves PCs diagnosis. For PC presented by focal asymmetry, MRS in the current study showed malignant spectral pattern at the bulky area, while, based on morphologic imaging alone such tumors were missed **(Fig. 3).**

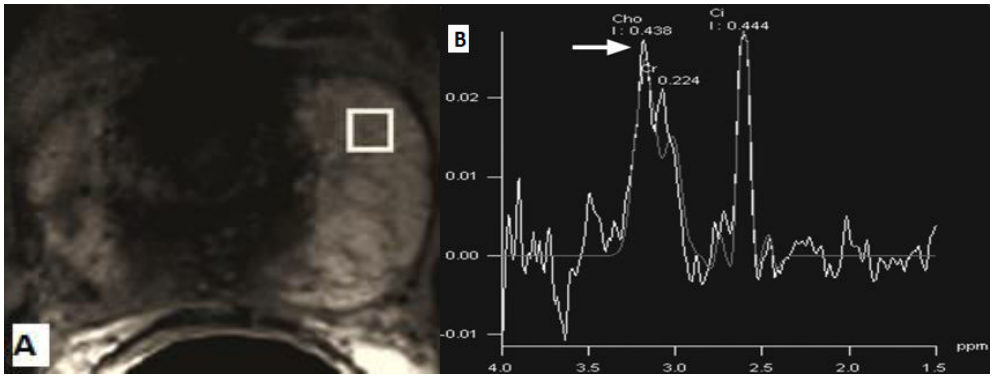

Fig.3. Endorectal MR imaging for 67 years old male patient with left PZ prostate adenocarcinoma:(A) Axial T2WI; the left PZ is enlarged compared with the right PZ, with no focal low signal intensity areas and patchy low areas in the right PZ. (B) MR spectroscopic spectrum from the voxel of interest shows malignant criteria of elevated level of choline (Cho) (arrow) that is almost equal to the citrate (Ci) peak with Cho + Cr/Cit ratio (1.49).

Differentiating PC from granulomatous prostatitis is one of the most challenging of MRI. In this study, prostatitis lesions mimicked PC on both T2 and DWI and were reported as PC. While their (Cho + Cre) /Cit) ratio was normal or mildly elevated but still significantly lower than those of malignant lesions with 50% of cases was correctly diagnosed on MRS as benign tissue (PI-RAD 2) and 50% was diagnosed as possible malignant tissue (PI-RAD 3) **(Fig. 4).**Our results are consistent with those of **Zabihzadeh et al.,2020**. They used Cho+Cr/Cit ratios > 0.58 for PC diagnosis and reported statistically significant higher mean ratios of Cho+Cr/Cit in PC than in prostatitis (1.54 ± 0.63 and 0.83 ± 0.48 respectively). Sensitivity, specificity, accuracy, PPV and NPV of MRS were 94.4%, 80%, 96%, 85% and 92.4%, respectively.

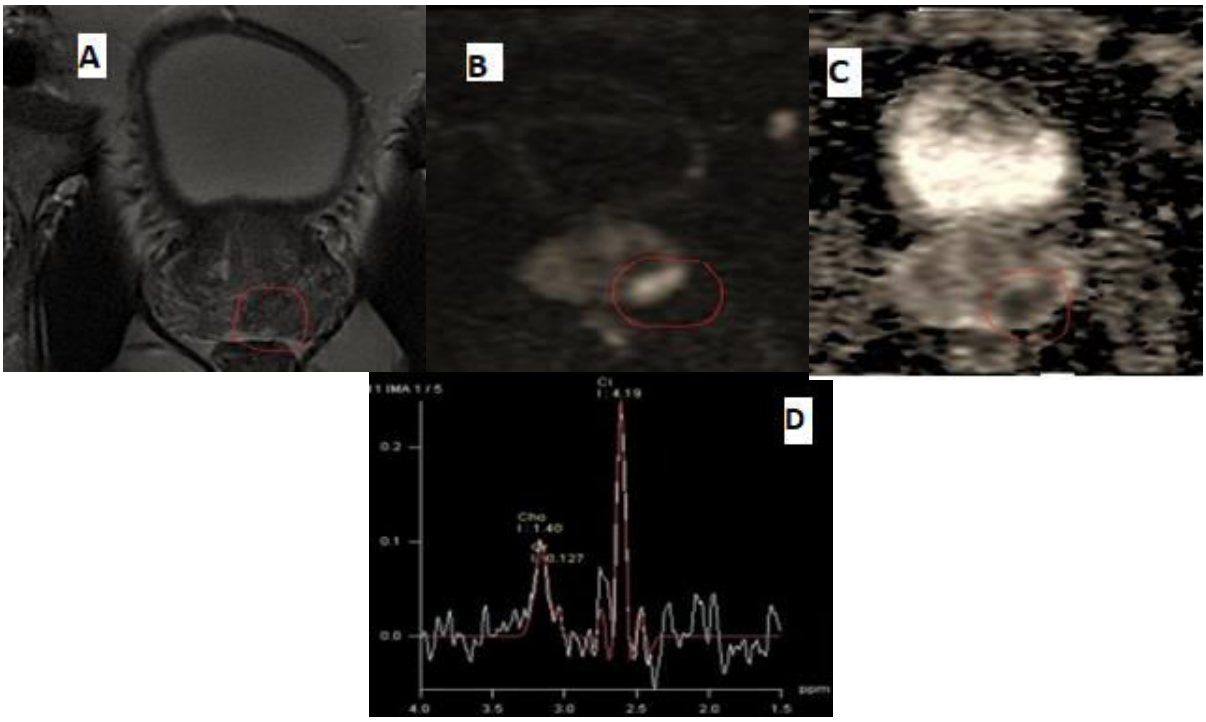

Fig. 4.45 years old male patient with granulomatous prostatitis: Focal highly suspicious lesion in the left posterior and postero-lateral PZ base (encircled) of homogenous hypo intense signal on axial T2WI **(A).** Restricted diffusion on DWI of bright signal **(B)** and low on ADC map with ADC value; $\pm$1.5 x 10^{-3} mm^2/s**(C).**MRS **(D)** shows benign spectrum as low peak value of choline and creatine and high peak value of citrate with low Cho + Cr/Cit Ratio (0.56).

MRS was very useful in detection of all cases of TZ carcinoma, showing elevated choline, reduced citrate peak and increased Cho+Cr/Cit ratio more than 0.94 (PI-RAD 5), while they were missed on T2 and DWI as the tumors within the TZ are challenging to detect, since the signal intensity overlap of normal TZ and cancerous tissue (**Lee et al 2016)** especially in cases of BPH where mixed and stromal BPH nodules may have low T2 signal intensity due to the presence of excess sclerotic, fibrous, or muscular

elements, restricted diffusion on DWI and show early enhancement on DCE images (**Kitzing et al., 2016**).

Considering prostatic atrophy, which is not always challenging on MRI (**Frenk NE, et al 2014**), combined T2 and DWI were not conclusive in our study while MRS showed their benign spectral pattern,(**Fig. 5**).

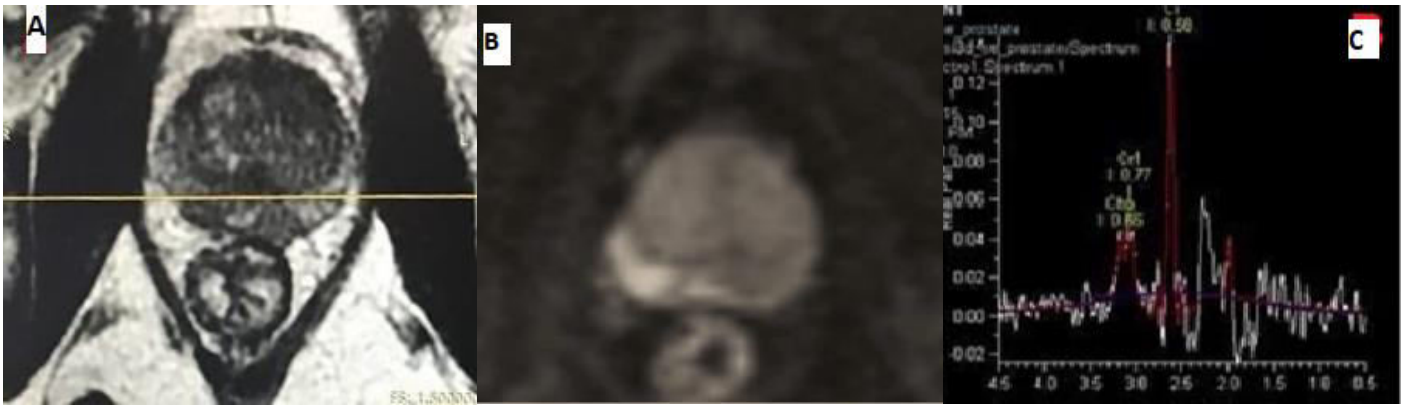

Fig.5. 53 years old male patient with biopsy-proved focal prostatic atrophy related to granulomatous prostatitis.(A) Axial T2WI: Patchy highly suspicious lesion in the posterior and R postero-lateral PZ base of homogenous hypo intense signal (B)DWI: mild corresponding restriction.ADC value; $\pm$1.35 x 10^{-3} mm^2/s(C)MRS:shows low peak value of choline and creatine and high peak value of citrate with Cho + Cr/Cit ratio (0.55).

On the other hand, prostatic infarctions were misdiagnosed on MRS as PI-RAD 3 and reported as possible malignant lesions, while they were correctly diagnosed by conventional MRI and DWI as initially, it has a hyperintense T1 signal and hypointense T2W images and isointense over time on both sequences (**Lovegrove et al., 2018**).

Conclusion

MRS –despite its limitations- Combined with T2WI and DWI is a promising diagnostic tool for better diagnosis of prostatic lesions compared to bpMRI (combined T2WI and DWI) especially in diagnosis of TZ carcinoma and PC presented with focal glandular asymmetry in addition to its role in differentiating PC from granulomatous prostatitis. MRS 100% negative predictive value for PC could avoid overdiagnosis and overtreatment. Further researches are recommended to reinforce the results of this study taking in consideration its limitations to detect MR Sutility in the clinical guidelines.

Study's limitations

Firstly, our results were obtained from a single institution study that may not be

generalized, but we aimed to have a homogeneous sample of MRI examination, to avoid possible bias from different MRI machines and different acquisition parameters. The second limitation is the relative small number of studied patients that may limit the ability to identify a statistically significant result. Further researches are needed, especially multicenter studies with attempt to reach an optimal MRS protocol for prostate MRI and thus assessment of the possibility of adding MRS to routine prostatic MR imaging.

Declarations

Ethical approval and consent to participate.

- The study was done according to the clinical research ethics of Sohag university hospital. The committee's reference number is not applicable not available.

Verbal consent was obtained from all included patients in the study because data and figures used in this study didn't include specific personal data or individual details refer to the person.

Consent for Publication.

- Consent for publication was obtained.

Competing interests.

- The authors declare that they have no competing interests.

Availability of data and materials

- The datasets used during the current study are available from the corresponding author on reasonable request.

Funding

-This work was not funded from any source.

Authors contributions

NMAH: Contributed in the design of the work, analysis and interpretation of data, writing the manuscript and have drafted the work and substantively revised it.MHA: Contributed in the design of the work and writing the manuscript.MAE: Contributed to the design of the work and data collection.MH: Contributed in the design of the work, and interpretation of data, and revised it. All authors have read and approved the manuscript.

Acknowledgements

Thanks for all technicians in MRI unit and our colleagues at Diagnostic Radiology Department. Shag Faculty of Medicine.

References

•**Barentsz JO, Richenberg J, Clements R,Choyke P, Verma S, Villeirs G, et al. (2012)** ESUR prostate MR guidelines 2012. EurRadiol 22:746–757.

• **Barrett T and Haider MA (2017)**The Emerging Role of MRI in Prostate Cancer Active Surveillance and Ongoing Challenges. AJR 208:131–139.

•**Bhatia C, Phongkitkarun S, Booranapitaksonti D, Kochakarn W, Chaleumsanyakorn P (2007)** Diagnostic accuracy of MRI/MRSI for patients with persistently high PSA levels and negative TRUS-guided biopsy results. J Med Assoc Thai. 90:1391–9.

• **Cancer Today- Global Cancer Observatory - International Agency for Research on Cancer IARC. (2020)** https://gco.iarc.fr/today.

• **Cirillo S, Petracchini M, Della MP, Gallo T, Tartaglia V, Vestita E, et al. (2008)** Value of endorectal MRI and MRS in patients with elevated prostate-specific antigen levels and previous negative biopsies to localize peripheral zone tumours. ClinRadiol. 63:871–9.

• **Destefanis P, Bosio A, De Maria C, Bisconti A, Cugiani A, Negro CLA, et al. (2009)** Targeted needle re-biopsy of the prostate after combination of endorectal MRI (ENDOMRI) and magnetic resonance spectroscopy (MRS) in patients with atypical small acinar proliferation (ASAP). EurUrol Suppl. 8:354.

• **Epstein JI. (2010)**The lower urinary tract and male genital system. In: Kumar V, Abbas AK, Fausto N, Aster JC. Robbins and Cotran Pathologic Basis of Disease. 8th ed. Philadelphia, PA: Saunders/Elsevier

• **Frenk NE, Baroni RH, Carnevale FC, Gonçalves OMG, Antunes AA, Srougi M, et al (2014)** MRI findings after prostatic artery embolization for treatment of benign hyperplasia. AJR Am J Roentgenol. Oct;203(4):813-21.

• **Fusco R, Sansone M, Granata V, Setola SV and Petrillo A (2017)** A systematic review on multiparametric MR imaging in prostate cancer detection. Infectious Agents and Cancer. 12:57.

• **Jagannathan D and Indiran V (2017)** Accuracy of Diffusion Weighted Images and MR Spectroscopy in Prostate Lesions – Our Experience with Endorectal Coil on 1.5 T MR. 10 Journal of Clinical and Diagnostic Research. May, Vol-11(5): 10-14.

• **Jemal A, Siegel R, Xu J, Ward E (2010)** Cancer statistics, 2010. CA Cancer J Clin 60:277–300.

• **KitzingYX, Prando A, Varol C, Karczmar GS, Maclean F, Oto A (2016)** Benign Conditions That Mimic Prostate Carcinoma: MR Imaging Features with Histopathologic Correlation. Radiographics. Jan-Feb 36(1):162-75.

• **Lahoti AM, Dhok AP, Rantnaparkhi CR, Rawat JS, Chandak NU, Tawari HS (2017)** Role of Magnetic Resonance Imaging, Magnetic Resonance Spectroscopy and Transrectal Ultrasound in Evaluation of Prostatic Pathologies with Focus on Prostate Cancer. Pol J Radiol. 82: 827-836.

• **Lee S, Joshi J, Wolfe K, Acher P, Liyanage SH (2016)** Radiologic presentation of chronic granulomatous prostatitis mimicking locally advanced prostate adenocarcinoma. Radiology case report 11(2) 78-82.

• **Li S, Chen M, Wang R, Zhou C (2007).**Differentiation between benign prostatic hyperplasia and prostate cancer in the transitional zone evaluated by 1H magnetic resonance

spectroscopic imaging. Chin Med Sci J Dec;22(4):238-42.

• **Lovegrove CE, Matanhelia M, Randeva J, Eldred-Evans D, Tam H, Miah S, et al (2018)** Prostate imaging features that indicate benign or malignant pathology on biopsy. TranslAndrol Urol. 7(Suppl 4):S420-S435.

• **Panebianco V, Sciarra A, Ciccariello M, Lisi D, Bernardo S, Cattarino S, et al. (2010)** Role of magnetic resonance spectroscopic imaging ([1 H]MRSI) and dynamic contrast-enhanced MRI (DCE-MRI) in identifying prostate cancer foci in patients with negative biopsy and high levels of prostate-specific antigen (PSA). Radiol Med. Dec;115(8):1314–29. 44.

• **Petrillo A, Fusco R, Setola SV, Ronza FM, Granata V, Petrillo M, et al. (2014)** Multiparametric MRI for prostate cancer detection: performance in patients with prostate-specific antigen values between 2.5 and 10 ng/mL.J MagnReson Imaging. May;39(5):1206–12.

• **PI-RADS. Prostate Imaging – Reporting and Data System (2019)** Version 2.1.

• **Sah VK, Wang L, Min X, Feng Z, Rizal R, Li L, et al.(2015)**Multiparametric MR imaging in diagnosis of chronic prostatitis and its differentiation from prostate cancer.Radiology of Infectious Diseases 1 70-77.

• **Sciarra A, Panebianco V, Ciccariello M, Salciccia S, Cattarino S, Lisi D, et al. (2010)** Value of magnetic resonance spectroscopy imaging and dynamic contrast enhanced imaging for detecting prostate cancer foci in men with prior negative biopsy. Clin Cancer Res. 16:1875–83.

• **Sciarra A, Panebianco V, Salciccia S, Osimani M, Lisi D, Ciccariello M, et al. (2008)**.Role of dynamic contrast-enhanced magnetic resonance (MR) imaging and proton MR spectroscopic imaging in the detection of local recurrence after radical prostatectomy for prostate cancer.Eur Urol. Sep;54(3):589–600.

• **Shukla-Dave A, Hricak H, Moskowitz C,Ishill N, Akin O, Kuroiwa K, et al. (2007)** Detection of prostate cancer with MR spectroscopic imaging: An expanded paradigm incorporating polyamines 1. Radiology. 245(2):499–506.

• **Stabile A, Giganti F, Rosenkrantz AB, Taneja SS, Villeirs G, Gill IS,et al. (2020)**Multiparametric MRI for prostate cancer diagnosis: current status and future directions. Nat Rev Urol. Jan;17(1):41-61.

• **Villeirs GM, De Meerleer GO, De Visschere PJ, Fonteyne VH, Verbaeys AC, Oosterlinck W (2011)** Combined magnetic resonance imaging and spectroscopy in the assessment of high grade prostate carcinoma in patients with elevated PSA: a single-institution experience of 356 patients. Eur J Radiol 77:340–345 29.

• **Wang P, Guo Y, Liu M, Qiang Y, Guo X, Zhang Y, et al (2008)** A Meta-Analysis of the Accuracy of Prostate Cancer Studies Which Use Magnetic Resonance Spectroscopy as a Diagnostic Tool. Korean J Radiol 9:432-438.

• **Weinreb JC, Blume JD, Coakley FV, Wheeler TM, Cormack JB, Sotto CK,et al. (2009)** Prostate cancer: sextant localization at MR imaging and MR spectroscopic imaging before prostatectomy: results of ACRIN prospective multi-institutional clinicopathologic study. Radiology 251:122–133

• **Wetter A, Hubner F, Lehnert T, Fliessbach K, Vorbuchner M, Roell S, et al. (2005)** Three-dimensional 1H-magnetic resonance spectroscopy of the prostate in clinical practice: technique and results in patients with elevated prostate-specific antigen and negative or no previous prostate biopsies. EurRadiol. 15:645–52.

• **Yu J, Fulcher AS, Turner MA, Cockrell CH, Cote EP, Wallace TJ.et al. (2014)** Prostate Cancer and Its Mimics at Multiparametric Prostate MRI. Br J Radiol. May 87(1037): 20130659. doi: 10.1259/bjr.20130659.

• **Zabihzadeh M, Asl J F, Farzanegan Z, Hoseini SM, Sarkarian M, Cheraghian B, Dahaz S, Garibvand MM (2020)** Accuracy of Magnetic Resonance Spectroscopy Techniques in Prostate Cancer and Prostatitis. Arch Iran Med. February 23(2):104-112.

• **Zhang T., Hu C., Chen J., Xu Z., Shen J.(2017)** Differentiation Diagnosis of Hypo-Intense T2 Area in Unilateral Peripheral Zone of Prostate Using Magnetic Resonance Spectroscopy (MRS): Prostate Carcinoma versus Prostatitis. Med SciMonit. 23: 3837-3843.