

## Multiparametric MRI for the Diagnosis of Tumor Type in Patients Suspicious of Inner Gland Prostate Cancer

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**Purpose:** The current study aimed to evaluate multiparametric MRI for the diagnosis of type of tumor (benign or malignant) in patients suspicious of inner gland prostate cancer.

**Materials and Methods:** This cross-sectional study was conducted on 44 consecutive patients with a clinical impression of prostate cancer who were referred to the MRI department of Payambaran Hospital, Tehran, Iran for confirmative diagnostic evaluation. Cases suspected of tumor relapse and those who previously underwent treatment for prostate cancer were excluded. Multiparametric MRI was performed for every patient by using a 1.5 Tesla device with an integrated endorectal and pelvic-phased array coil. All patients subsequently underwent MRI-transrectal ultrasound fusion biopsy. The diagnostic value of each sequence was then investigated individually and in combination with other techniques by comparing the results with histological findings from MRI-TRUS fusion biopsy.

**Results:** Among the techniques, T2-weighted imaging (T2W) had the highest sensitivity and specificity while dynamic contrast enhanced (DCE) technique had the least. Diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) had a similar sensitivity and specificity and did not significantly differ from T2W. Adding functional techniques to T2W did not improve diagnostic indices compared to T2W alone. Quantitative evaluation of apparent diffusion coefficient (ADC), DWI, and MRS showed that all techniques were able to differentiate between benign and malignant tumors. However, the quantitative combination of these sequences decreased diagnostic performance.

**Conclusion:** T2W is the best technique for the diagnosis of type of tumor in terms of benignancy or malignancy in patients suspicious of inner gland prostate cancer. Adding functional imaging measurements to T2W does not improve its diagnostic value.

**Keywords:** multiparametric MRI; prostate cancer; zone; T2 weighted imaging.

### INTRODUCTION

Cancer has become a major public health problem and accounts for the third leading cause of death in Iran. Specifically, prostate cancer has turned into an important issue in the world especially in developing countries. It is the second most prevalent cancer in the world and the sixth most prevalent in Iran. The most common histology observed in prostate cancer is adenocarcinoma which is also associated with a shorter life span.<sup>(1)</sup> Regarding zonal origin, 65% of prostate tumors originate from the peripheral zone while about 30% of them develop from the transition zone. The presence of transition zone tumors plays a significant role in the progression and mortality of the disease. Thus, the early diagnosis is essential.<sup>(2)</sup> Prostate cancer is initially diagnosed by measuring

prostate-specific antigen (PSA) level and performing digital rectal exam (DRE). Definite diagnosis is made through transrectal ultrasound-guided (TRUS) biopsy. However, these diagnostic techniques have some drawbacks. Low sensitivity and low positive predictive value (PPV) of DRE, low specificity of PSA measurement, and inefficacy of systemic biopsy in diagnosing cancers of the anterior part of the prostate are some of the limitations related to these methods. Hence, identifying a non-invasive and more precise method for early diagnosis of prostate cancer is crucial.<sup>(3)</sup>

In the mid-1980s, for the first time T1-weighted (T1W) and T2-weighted (T2W) imaging techniques of MRI were used for prostate imaging. Gradually, by adding functional imaging (DWI, DCE, and MRS) to the anatomic sequence (T2W), it became possible to examine

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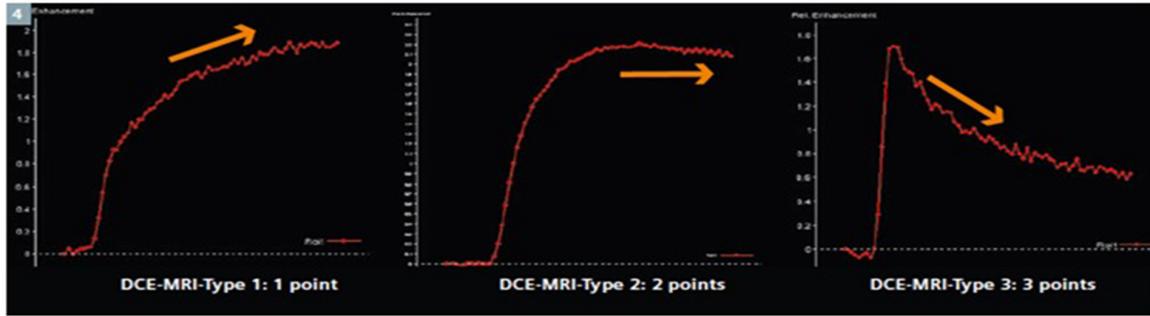
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**Figure 1.** Classification of DCE

- I: Slow entrance of the contrast agent and contrast is kept being enhanced and having the same signal with background tissue
- II: Rapid entrance and relatively rapid exit of the contrast agent from tissue
- III: Very rapid entrance and exit of the contrast agent from tissue

the physiological properties of tissues. Among these functional parameters, dynamic contrast enhanced (DCE) is efficient for assessing microvascular properties, diffusion weighed imaging (DWI) is sensitive to the restriction of water molecule diffusion movement and magnetic resonance spectroscopy (MRS) is valuable for evaluating biochemical changes within the prostate tissue. However, none of these functional techniques are sufficient for the diagnosis of prostate cancer individually. Moreover, heterogeneous appearance and overlap enhancement of BPH nodules originating from the transition zone complicates the detection of tumors originating from this zone.<sup>(3,4)</sup>

The current study was conducted to evaluate the efficacy of multiparametric MRI (mpMRI) for the diagnosis of type of tumor in the inner prostate gland (transition, central, and fibromuscular zone). Also, we aimed to compare the results obtained from MRI with the results of MRI-TRUS fusion biopsy as it is considered the golden standard of diagnosis.

**MATERIALS AND METHODS**

**Study Design, Sample and Population**

This cross-sectional study was performed during 2017 on patients clinically suspicious of prostate cancer who were referred to the MRI department of Medical Imaging Center of Payambaran Hospital, Tehran, Iran for further diagnostic evaluation. Sample size was computed by using PASS software (version 11.0.4). A sample size of n=44 was required to achieve 80% power for the two-sided binomial test to detect a change in sensitivity from 0.5 to 0.8. The probability of type one error (α) was considered to be 0.05. Also, based on previous

studies, the prevalence of prostate cancer was estimated to be 0.50.<sup>(5)</sup> The present research was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (ethics code: IR.SBMU.RETECH.REC.1396.828).

**Inclusion and exclusion criteria**

This study included men ≥ 50 years old with a clinical suspicion of prostate cancer who were referred by an urologist for MRI imaging and prostate biopsy. The primary diagnosis was based on an increase in the serum level of PSA (PSA> 3ng/mL) or an abnormal DRE. Exclusion criteria included tumor relapse, having already undergone treatment, and having contraindications for receiving endorectal coil such as presence of severe hemorrhoid or severe inflammatory bowel disease, sensitivity to latex, or history of rectal resection. Subjects who were contraindicated for MRI imaging (i.e. presence of ferromagnetic implants and cardiac pacemakers) or gadolinium contrast agent injection (i.e. active asthma, allergy to gadolinium, severe allergy, and GFR < 30 ml/min) were also excluded from the study. In addition, cases whose obtained images were not satisfactory (e.g. multiple artifacts due to total hip replacement or patient movements) were also not included.

**Procedures**

In this study, an MRI scanner with a field strength of 1.5 Tesla (Magnetom Avanto, Siemens) along with combined endorectal and pelvic phased-array coils was used. Multiparametric sequences including T2W, DWI, DCE, and MRS were performed for all patients. The detail of each protocol is shown in **Table 1**. For DCE MRI, 0.1 mmol/kg gadolinium contrast agent was ad-

**Table 1.** Details and parameters of the sequences

Pulse sequences	T1-W (TRA)	T2-W(TRA-SAG-COR)	DWI (TRA)	DCE (TRA)	MRS (3D-CSI)
Time Repetition (ms)	600	8000	4400	4.96	650
Time Echo (ms)	12	109	82	1.69	120
(mm)slice thickness	3	3	3	3	-
Matrix size	256×192	320×320	102×50	192×138	-
number of section	24	24	30	28	10
Field Of View(mm)	175×175	175 ×175	175×85	250×250	190×190
Flip Angle	150	150	-	12	90-180-180
Average (NEX)	1	1	6	1	8
(mm) voxel size	0.9×0.7×3	0.5×0.5×3	1.7×1.7×3	1.9×1.4×3	10×10×10
Temporal resolution	-	-	-	11s	-
b-value(s/mm <sup>2</sup> )	-	-	50-400-800-1200	-	-

**Table 2.** Diagnostic indices of T2-W, DCE, DWI, and MRS

Sequences	sensitivity	specificity	Positive Predictive Value	Negative Predictive Value	Precision
T2-W	81.8% (18/22)	95.5% (21/22)	94.7% (18/19)	84% (21/25)	88.6% (39/44)
DWI	72.7% (16/22)	86.4% (19/22)	84.2% (16/19)	76.0% (19/25)	79.5% (35/44)
DCE	59.1% (13/22)	54.5% (12/22)	56.5% (13/23)	57.1% (12/21)	56.8% (25/44)
MRS	71.4% (15/21)	90.5% (19/21)	88.2% (15/17)	76.0% (19/25)	81.0% (34/42)

**Abbreviations:** T2-W: T2-weighted; DWI: Diffusion Weighted Imaging; DCE: Dynamic Contrast Enhanced; MRS: Magnetic Resonance Spectroscopy

ministered with an injection rate of 2-3 ml/s followed by 20 mL normal saline flush. The temporal resolution was equal to 11 seconds.

#### Evaluations

Initially, an experienced radiologist interpreted the MRI images and correlated the lesions observed in T2W with functional sequences. Diagnostic characteristics for the detection of tumoral lesions included lesion morphology and homogeneous low signal intensity in T2W, restricted diffusion in DWI, early enhancement and wash out of the contrast agent in dynamic imaging, and increase in the choline + creatinine to citrate ratio (Cho + Cr/Ci) in MR spectroscopy. According to the PI-RADS v2 scoring system, findings of T2W and DWI were assessed on a 5-point category scale with 5 being most likely to represent clinically significant prostate cancer. MRS was also assessed with a score from 1 to 5. DCE was evaluated based on the shape of the curves (**Figure 1 and 2**). MRI- TRUS fusion biopsy was considered as the gold standard of diagnosis.

Considering the correlation between the imaging scores and the results obtained from fusion biopsy, the scores of 1 and 2 were considered as negative, score 4 and 5 as positive, and the score of 3 was considered negative for T2W and DWI and positive for MRS. As for the DCE technique, asymmetry and focal early enhancement were assumed to be positive along with the shape of plateaus and washout.

In the second stage of evaluation, quantitative and semi-quantitative values were obtained using the syngo MRI software (Siemens Medical Solutions), spectroscopy software, and mean curve. Quantitative factor of diffusion coefficient, the ratio of metabolites in MRS and TIC pattern diagrams were considered as quantitative and semi-quantitative values.

Advanced ultrasound devices that were equipped with special software and hardware to accurately match MRI images with ultrasound images were used for tissue sampling. With the help of the sensors connected to the ultrasound probe and the patient's body, the probe's position relative to the prostate was detected at any time and by moving the probe in different directions within the rectum, an ultrasound image was provided on the monitor as well as an equivalent MRI image. By marking the suspicious mass on the MRI image, the same

area was automatically marked on the ultrasound image, and the corresponding software specified the needle pathway to obtain a tissue sample from the mass. Then, samples were sent for pathological evaluation.

#### Statistical Analysis

Analysis was performed using SPSS software version 20 (IBM, Chicago, Illinois, USA) and MedCalc version 12.1.4 (MedCalc Software bvba, Mariakerke, Belgium). Diagnostic indices including the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, ROC curve, and area under the curve (AUC) of each sequence was calculated separately. McNemar's test was employed for the comparison of diagnostic values and logistic regression model was used for the evaluation of combined MRI sequences.  $P$ -value < .05 was considered as statistically significant.

## RESULTS

A total of 44 male patients suspicious of prostate cancer with a mean age (SD) of 65.1(5.9) years old (range: 53 – 80) and a serum PSA level > 3 ng/mL were included in the study. Based on histological examination, 22 patients (50%) were diagnosed with malignancy with a Gleason Score  $\geq$  6 and the rest had benign tumors.

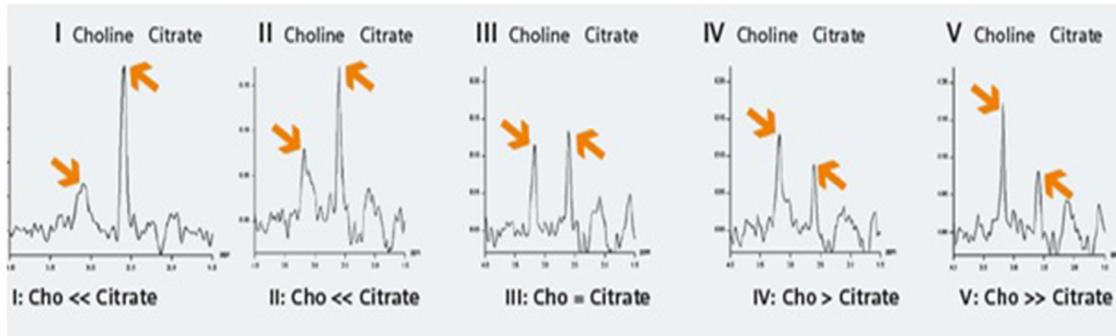
Regarding the ability of each technique to detect the type of tumor separately, results obtained from imaging with T2W, DCE, DWI and MRS (qualitative) sequences were not compatible with histologic findings in 5,19,9, and 9 cases, respectively. **Table 2** reports the diagnostic indices of these sequences when performed in isolation. There was a significant difference between the specificity of DCE and T2W techniques only ( $P = .004$ ). As shown in **Figure 3**, T2W had a greater AUC compared to the other techniques. The estimated AUC was equal to 0.89 ( $P < .001$ ), 0.57 ( $P = .44$ ), 0.80 ( $P = .001$ ), and 0.80 ( $P = .001$ ) for T2W, DCE, DWI, and MRS sequences, respectively.

The results for double, triple, and quadruple combinations of the aforementioned techniques (T2W+DWI, T2W+MRS, T2W+DCE, T2W+DWI+DCE, T2W+DWI+MRS, T2W+DWI+DCE +MRS) were found to be similar to those of T2W alone ( $P > 0.05$ ). In other words, by adding functional sequences to T2W, no changes were observed in terms of diagnostic indices. The techniques of DWI, ADC, and MRS were also investigated quantitatively (**Table 3**). Quantitative investigation of DWI, ADC map showed that the results obtained from these parameters were not compatible with histological findings in 14 cases (31.8%). Sensitivity, specificity, PPV, NPV, and accuracy were reported to be 63.6, 72.7, 70, 66.7, and 68.2%, respectively. Considering the ROC curve, the AUC was calculated as 0.73, which was statistically significant ( $P = .003$ ). On this basis,  $648 \times 10^{-6}$  was determined as the cut-off point for differentiation of benign lesions

**Table 3.** Descriptive indices for mean ADC and quantity of MRS

Descriptive indices	Mean ADC <sup>1</sup>	Quantity of MRS <sup>2</sup>
Mean	684.6 $\times$ 10 <sup>-6</sup>	1.14
Standard Deviation	138.9 $\times$ 10 <sup>-6</sup>	1.47
minimum	402 $\times$ 10 <sup>-6</sup>	0.02
maximum	978 $\times$ 10 <sup>-6</sup>	7.16

1: Apparent diffusion coefficient; 2: Magnetic resonance spectroscopy



**Figure 2.** Classification of MRS  
 I: Cho is significantly lower than citrate (<<)  
 II: Cho is elevated but still lower than citrate (<)  
 III: Cho is approximately on the same level as citrate (=)  
 IV: Cho is elevated compared to citrate (>)  
 V: Cho is significantly elevated compared to citrate (>>)

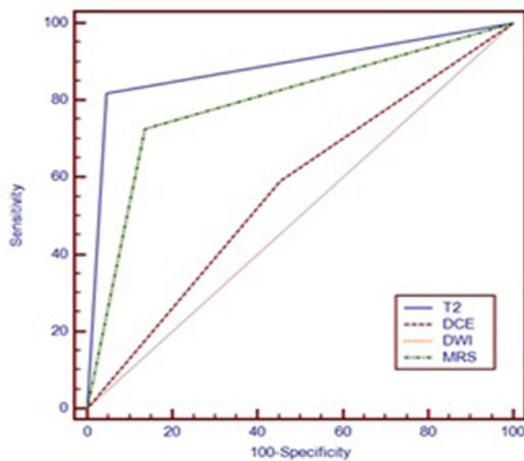
from malignant ones. The quantitative investigation of MRS showed that the results were not compatible with pathology findings in 11 cases. Sensitivity, specificity, PPV, NPV, and accuracy were reported as 68.2, 81.8, and 78.8, 72, and 75%, respectively. Considering the ROC curve, the AUC was calculated as 0.73 which was statistically significant ( $P = .004$ ). Based on this result, 0.91 was determined as the cut-off point for differentiation of benign lesions from malignant types.

Our results showed that there was no significant difference between ADC and MRS in diagnosing the type of tumor ( $P = .97$ ). The mean ADC and the quantity of MRS were combined together. The results of this combination in diagnosing the type of tumor were not compatible with the pathology findings in 18 cases. Sensitivity, specificity, PPV, NPV, and accuracy were reported to be 59.1%, respectively. The AUC was also estimated as 0.59, which was not statistically significant ( $P = .23$ ) (Figure 4).

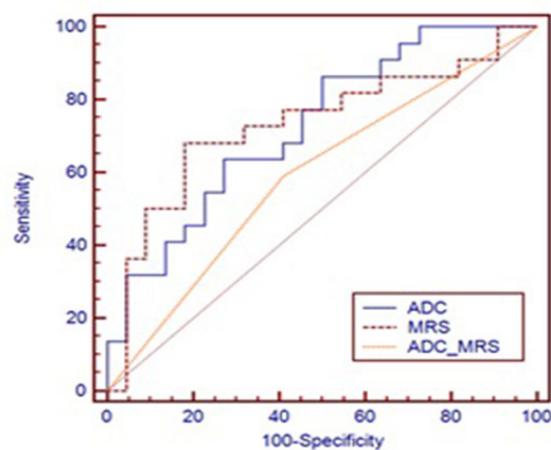
**DISCUSSION**

The current study was carried out to evaluate the di-

agnostic indices of mpMRI for detection of malignant or benign type of tumor in patients suspicious of inner gland prostate cancer. Our results indicated that T2W had the highest sensitivity and specificity while DCE had the least. The sensitivity and specificity of qualitative DWI and MRS techniques were found to be similar. DWI and MRS were not significantly different compared to T2W. However, DCE specificity had a significant difference compared to T2W. Each of these techniques might report false positive results because of the difficult differentiation between prostate cancer and benign hyperplasia. Due to the hypervascularity of BPH in DCE and the low amount of ADC in DWI and ADC maps, there is an overlap between the amounts of ADC in stromal BPH with the amounts in prostate cancer.<sup>(4,6,7)</sup> In addition, based on the data obtained from DCE imaging, 9 of the 22 cases with malignant lesions had persistent enhancement which might be attributed to the presence of fewer arteries in the tumor.<sup>(8)</sup> In MRS, the different amount of metabolites in various parts of the prostate (such as the difference in the peri-urethral zone from other zones or the higher citrate concentra-



**Figure 3.** ROC curve for comparison of the diagnostic value of the three sequences of DWI, DCE, and MRS with the sequence of T2 in diagnosing the type of tumor



**Figure 4.** ROC curve for comparison of mean ADC, MRS, and combination of mean ADC, MRS

tion in glandular proliferation) as well as the extensive range of metabolites in tumors of the internal portion of prostate may result in false positive results.<sup>(9,10)</sup> The sensitivity and specificity of T2W were the highest which could be due to anatomical characteristics.<sup>(11)</sup> Nonetheless, benign lesions such as chronic inflammation of the prostate, atrophy, scar, benign hyperplasia of the prostate, post-biopsy bleeding, and the effects of hormone therapy or radiotherapy can mimic the tumor tissue in T2W. In this study, the number of false positive cases in T2W reduced with the use of MRI at appropriate time intervals with respect to previous biopsy and also elimination of patients who had received previous treatment. Our findings also indicated that adding functional techniques to T2W does not improve diagnostic indices of the inner gland. Regarding mpMRI, our results are in agreement with the studies by Delongchamps et al.<sup>(3)</sup> and Hoeks et al.<sup>(2)</sup> Li et al. (2006) indicated that adding DCE to T2W increased the diagnostic precision of prostate cancers within the transition zone.<sup>(12)</sup> Puech and colleagues investigated the diagnostic value of DCE and the consequences of its elimination from mpMRI. They showed that this technique is able to identify undetectable lesions on T2W and DWI.<sup>(13)</sup> However, in the present study, DCE had the lowest diagnostic value and its addition to T2W did not increase diagnostic performance. Meanwhile, based on the results, there was no lesion identified by DCE which had not been observed on T2W. Hong Li et al. considered monotonous low intensity signal on T2W, homogeneous enhancement in DCE, and irregular margins between the lesion and the central zone on T2W and DCE which could not be easily detected in T2W, sometimes, in favor of cancer. However, in the present study, the diagnostic value of DCE was based on the TIC curve, ascribing to the differences in methodologies.

The results of this study indicated that T2W and DWI techniques were appropriate for detection of type of tumor within the transition zone, but DCE did not provide any further information. Meanwhile, gadolinium increases the time and cost of the test.<sup>(14-17)</sup>

In the present study, in addition to the qualitative investigation of DWI, the intensity of the signal was achieved by drawing regions of interest (ROI) on ADC maps of the lesion. This measure shows the degree of diffusion of water molecules. In scientific terms, the diffusion of water molecules is more restricted in malignant lesions and so, the signal intensity decreases in greater quantities.<sup>(2)</sup> This quantitative evaluation stated that the mean ADC is useful in differentiating between benign and malignant tumors which is in line with a qualitative study by Schimoller et al (2014).<sup>(18)</sup>

Our findings also revealed that quantitative MRS was able to differentiate between benignancy and malignancy. The comparison between mean ADC and MRS quantity indicated that the two techniques were not significantly different in diagnosing the tumor type. In addition, the combination of mean ADC and MRS quantity showed weakness in differentiating benign from malignant lesions. However, more data is needed for a more accurate report.

There were some limitations in the present study. Our sample size was restricted due to the fact that the prevalence of transition zone tumor is much less than peripheral zone tumor which makes it difficult to collect more samples in a limited time. Second, the results of

DCE and TIC curve obtained from mean curve software might have been different if another type of software was used. The third limitation was related to the gold standard diagnosis method. mpMRI TRUS fusion biopsies improve the detection of clinically significant cancers compared to systematic TRUS-guided biopsies, however, fusion biopsies alone fail to diagnose 8.3% of cancers including 6.7% of significant cancers.<sup>(19)</sup>

## CONCLUSIONS

The results of this study showed that T2W is the best MRI imaging technique for the diagnosis of type of tumor in the inner gland of prostate. Adding functional techniques did not increase the diagnostic value of tumor detection in this zone.

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## CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this paper.

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