Original Article

A prospective study of the efficacy of magnetic resonance spectroscopy imaging for predicting locally advanced prostate cancer

Lokal ilerlemiş prostat kanserini öngörmede manyetik rezonans spektroskopi görüntülemenin etkinliği üzerine prospektif bir çalışma

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ABSTRACT

Objective: To evaluate the efficacy of magnetic resonance spectroscopy imaging (MRSI) for predicting locally advanced prostate cancer (PC).

Material and methods: Between April 2009 and July 2012, 80 consecutive patients with clinically localized PC had undergone endorectal MRSI before radical retropubic prostatectomy. Clinicopathological parameters, including age, preoperative prostate-specific antigen (PSA), Gleason score (GS) at biopsy, perinural invasion at biopsy, prostate weight at surgery, GS of surgical specimen, and pathological staging were recorded. The MRSI findings were compared with the histopathological findings of the radical prostatectomy. The diagnostic accuracy measures consisting of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of MRSI, and other variables in the diagnosis of locally advanced PC (Pathology Stages pT3a, pT3b, or pT4) were evaluated.

Results: Sensitivity, specificity, PPV, and NPV of MRSI in detecting locally advanced PC is 42.4%, 93.6%, 82.3%, and 69.8%, respectively [area under the receiver operating characteristic (ROC) curve=0.658, p value <0.0001]. MRSI, cancer-positive core percentage at biopsy, and GS at biopsy are more accurate factors among all the predictive variables in predicting locally advanced PC.

Conclusion: MRSI may be considered as a complementary diagnostic modality with high specificity and moderate sensitivity in predicting locally advanced PC. Combination of this modality with other predictive factors helps the surgeon and patient to select an appropriate treatment strategy.

Keywords: MRS; prostate cancer; radical prostatectomy.

ÖZET

Amaç: Lokal ilerlemiş prostat kanseri (PK)'ni öngörmede manyetik rezonans spektroskopi görüntüleme (MRSG)'nin etkinliğini değerlendirmek.

Gereç ve yöntemler: Nisan 2009 ve Temmuz 2012 arasında, klinik olarak lokalize PK'sı olan 80 ardışık hastaya radikal retropubik prostatektomi öncesi endorektal MRSG uygulandı. Yaş, preoperatif prostat spesifik antijen (PSA), biyopside Gleason skoru (GS), biyopside perinural invazyon, cerrahide prostat ağırlığı, cerrahi numunenin GS ve patolojik evreleme dahil olmak üzere klinikopatolojik parametreler kaydedildi. MRSG bulguları radikal prostatektomi histopatolojik bulguları ile karşılaştırıldı. Lokal ilerlemiş PK tanısında MRSG'nin duyarlılık, özgüllük, pozitif prediktif değer (PPV), negatif prediktif değer (NPV)'den oluşan tanısal doğruluk ölçümleri ve diğer değişkenler (Patoloji Evreleri pT3a, pT3b veya pT4) değerlendirildi.

Bulgular: Lokal ilerlemiş PK'nin saptanmasında MRSG'nin duyarlılık, özgüllük, PPV ve NPV değerleri sırasıyla %42,4, %93,6, %82,3 ve %69,8 idi [alıcı işletim karakteristiği (ROC) eğrisi altında kalan alan =0,658, p değeri <0,0001]. Lokal ilerlemiş PK'yi öngörmede tüm prediktif değişkenler arasında MRSG, biyopside kanser pozitif çekirdek yüzdesi ve biyopside GS daha doğru faktörlerdi.

Sonuç: MRSG lokal ilerlemiş PK'yi öngörmede yüksek özgüllük ve orta düzeyde duyarlılık ile bir tamamlayıcı tanı yöntemi olarak kabul edilebilir. Diğer prediktif faktörlerle birlikte bu yöntemin kombinasyonu uygun bir tedavi stratejisi seçmek için cerrah ve hastaya yardımcı olur.

Anahtar kelimeler: MRS; prostat kanseri; radikal prostatektomi.

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Introduction

Prostate cancer (PC) is the second most common cancer in men worldwide.[1] The initial tests in the detection and staging of PC includes digital rectal examination, obtaining serum prostate-specific antigen (PSA), transrectal ultrasound (TRUS), and TRUS-guided

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biopsy. The preferred method for treatment of locally advanced PC is controversial. Consequently, prior to administering a treatment, accurate staging of PC is important for selecting the appropriate treatment modality in patients with PC. Despite limitations of computed tomography (CT), ultrasonography and magnetic resonance imaging (MRI) are helpful imaging modalities in staging PC.[2] Recent improvement in MRI techniques resulted in the development of more accurate modalities in the evaluation of PC.[3-7] For example, magnetic resonance spectroscopic imaging (MRSI) with an endorectal coil is considered as a more accurate imaging modality in the evaluation of PC.[3,6-8] In this study, we evaluate the value of MRSI in the detection of PC extracapsular extension.

Material and methods

Patient population

A prospective study was conducted by including 80 consecutive patients with clinically localized PC who had undergone endorectal MRSI before radical retropubic prostatectomy (RRP). This prospective study was approved by the Ethics Committee of the Tehran University of Medical Sciences. The diagnosis of PC was suspected by the measurement of serum PSA level and digital rectal examination and confirmed using TRUS-guided biopsy. Pretreatment evaluation included serum PSA level measurement, TRUS-guided biopsy, whole body bone scan (if PSA >10), and chest X-ray imaging for all studies. None of the patients received any type of PC treatment prior to the study. Clinicopathological parameters from April 2009 to July 2012, including age, preoperative PSA, Gleason score (GS) at biopsy, perineural invasion (PNI) at biopsy, GS of surgical specimen, and pathological staging were recorded. Written informed consent was obtained from patients who participated in this study.

MRSI technique

Prior to RRP, all patients underwent MRI of the prostate gland with and without contrast with endorectal coil and multivoxel H1 MRSI using Siemens Magneto Avanto 1.5 T, 18 Channel T-Class magnetic resonance machine. The mean time interval from performing biopsy to MRSI was 2 weeks (range: 1–4 weeks).

Histopathological interpretation

All patients with non-metastatic PC underwent open RRP by one surgeon. After formalin fixation, all specimens were sent to the pathologist and classical step section sextant histopathology analysis was performed. Each patient was staged based on the 2010 tumor, node, and metastasis (TNM) American Joint Committee on Cancer (AJCC).

Data interpretation

One experienced general radiologist interpreted all imaging and was unaware of the histopathological finding of the patients. The entire prostate gland and surrounding tissue were evaluated on MRI. Suspicious hypo-intense lesions that showed enhancement after contrast injection were suggestive of PC. With the H1 Spectroscopy, a significant rise in the choline/citrate ratio (score 4 or 5 according to the five-point standardized scoring system) was detected in the prostate gland which confirmed PC.[6] The capsule of prostate, periprostatic fat, neurovascular bundles, seminal vesicles, and Denonvilliers' fascia were evaluated for tumor involvement. The staging of PC took place based on the TNM staging [The latest modification by the AJCC (2010)]. Tumor aggressiveness was evaluated according to the primary and secondary Gleason grades. Correlations between tumor locations on MRSI and location on step-section pathology maps were performed. The MRSI findings were compared with the histopathological findings of the radical prostatectomy. The diagnostic accuracy measures including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of variables in the diagnosis of locally advanced PC (Pathology Stages ≥PT3) were also evaluated.

Statistical analysis

Data were analyzed by Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) software version 16.0. The diagnostic accuracy including sensitivity (number of true positive/number of true positive + number of false negative), specificity (number of true negative/number of true

Table 1. Patient and tumor characteristics

Characteristic	Value
Age, mean±SD (range), years	63.5±7.7 (46–78)
Perineural invasion at biopsy, No. of patients (%)	41 (51)
Preoperative serum PSA, mean±SD (range), ng/mL	16.3±19 (2.1–96)
Gleason score at biopsy, No. of patients (%)	
<7	35 (43.8)
3+4	25 (31.2)
4+3	13 (16.2)
>7	7 (8.8)
Percentage of cancer-positive core specimens in all core biopsy specimens, mean±SD(range)	47.8±27 (5–100)
Tumor volume, mean±SD (range), %	37.3±23.2 (2–90)
Pathological Gleason score, No. of patients (%)	
BPH	2 (2.5)
<7	35 (43.8)
3+4	17 (21.2)
4+3	9 (11.2)
>7	17 (21.2)

BPH: benign prostatic hyperplasia; prostate-specific antigen; SD: standard deviation

negative + number of false positive), PPV (number of true positive/number of true positive + number of false positive), and NPV (number of true negative/number of true negative + number of false negative) of MRSI in the diagnosis of locally advanced PC (Pathology Stages ≥PT3) were calculated. We evaluated possible predictor variables such as age, serum PSA level, GS at biopsy, percentage of cancer-positive core specimens in all core biopsy specimens, and presence of perineural invasion (PNI) at biopsy. Logistic regression analysis was applied to evaluate the effect of each variable in predicting locally advanced PC. The area under the receiver operating characteristic (ROC) area under the curve (AUC) was calculated for each variable. A p value less than 0.05 were considered statistically significant.

Results

Eighty patients with non-metastatic PC underwent MRI/MRSI and then RRP in our prospective study. Patients' demographic and clinicopathological characteristics are shown in Table 1. In addition, Table 2 demonstrates the distribution of MRSI tumor staging and final pathologic tumor stages. In logistic regression analysis of predictive variables, the evaluated items except patients' age were associated with the prediction of locally advanced PC (Table 3). Figure 1 presents the ROC curve for the evaluated variables in predicting locally advanced PC. The greatest AUC (better prediction performance) was related to the cancer-positive core percentage at biopsy (0.771). MRSI acquired the third rank of AUC among the predictive variables after cancer-positive core percentage at biopsy and GS at biopsy. According to the ROC curve, the greatest degree of predicting the performance of variables such as PSA, cancer-positive core percentage at biopsy, and GS at biopsy in predicting locally advanced PC are achieved when PSA >8.1 ng/mL, cancer-positive core percentage >47%, and GS at biopsy >3+4. In brief, our study showed that MRSI, cancer-positive core percentage at biopsy, and GS at biopsy are more accurate factors among all predictive variable in detecting locally advanced PC. Sensitivity, specificity, PPV, and NPV of MRSI in detecting locally advanced PC are 42.4%, 93.6%, 82.3%, and 69.8%, respectively (AUC=0.660, p value=0.001).

Table 2. Distribution of magnetic resonance spectroscopy imaging tumor staging and final pathologic tumor stages

MRSI tumor stage, No of patients	Pathological tumor stage, No of patients				
	BPH*	T2	T3	T4	Total
No tumor	0	0	1	0	1
T2	2	42	14	4	62
T3	0	3	9	3	15
T4	0	0	1	1	2
Total	2	45	25	8	80

BPH: benign prostatic hyperplasia; MRSI: magnetic resonance spectroscopy imaging

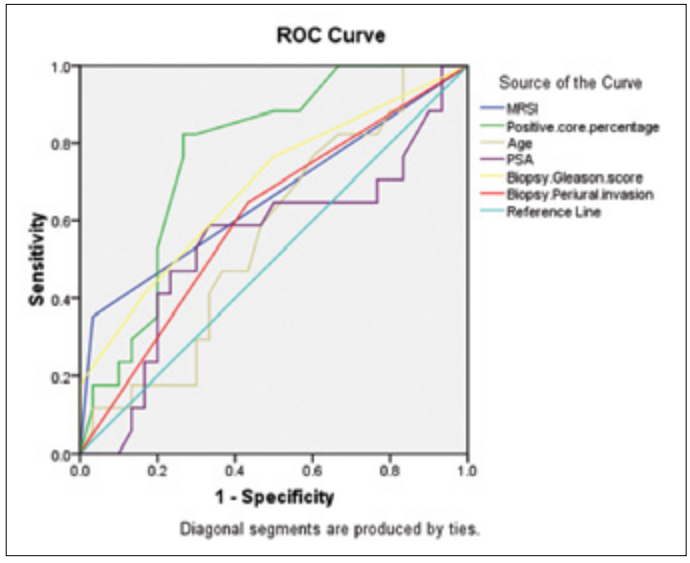

Figure 1. ROC curve for variables in predicting locally advanced PC

ROC: receiver operating characteristic; PC: prostate cancer

Table 3. Logistic regression analysis of factors predicting locally advanced prostate cancer

Variable	p value	Odds ratio (95% CI)	Area under ROC curve
Patient age	0.685	1.01 (0.955–1.07)	0.565
Serum PSA level	0.046	1.03 (1.00–1.06)	0.546
Perineural invasion at biopsy	0.046	2.94 (0.97–8.89)	0.607
Gleason score at biopsy	0.002	2.40 (1.38–4.17)	0.686
Cancer-positive core percentage at biopsy	0.001	1.04 (1.01–1.06)	0.771
MRSI	0.001	10.8 (2.77–42.02)	0.660

ROC: receiver operating characteristic; PSA: prostate-specific antigen; MRSI: magnetic resonance spectroscopy imaging

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Discussion

Approximately 90% of men diagnosed with PC have clinically localized disease. Radical prostatectomy is the gold standard treatment modality for localized PC, providing the best results with respect to cancer control. However, the preferred method for treatment of locally advanced PC is controversial. Consequently, accurate pretreatment tumor staging, particularly differentiating local PC from advanced PC, plays an important role in the selection of the appropriate treatment strategy. Several diagnostic procedures with different accuracy rate have been used for local tumor staging of PC.[9-11] One such modality is CT. The main role of CT in the evaluation of PC is nodal staging and detection of local advancement of tumor to adjacent structures; however, it has no significant efficacy in the assessment of primary tumors.[11] MRI has been utilized to diagnose and stage PC.[11-13] Some investigators reported a 13%–95% sensitivity and a 49%-97% specificity for MRI in the detection of extracapsular extension (ECE).[9] Developments in MRI technology improved tumor localization and detection of ECE.[11]

Magnetic resonance spectroscopy imaging is a new technology in MRI that evaluates metabolic changes, including choline, citrate, and creatine levels, among tumoral tissues. A significant rise in choline and creatinine to citrate ratio (Cho+Cr/Cit) is associated with the detection of PC. Diagnostic cutoff points for this ratio are different in central and peripheral zones and also different among investigators. Hence, the Five-point standardized scoring system has been used as an accepted scoring system among uro-radiologists.[6]

Jambor et al.[14] evaluated the ability of 11C-acetate PET/CT, MRI, and MRSI to capture images of localized PC and identify its aggressiveness in a prospective study. They enrolled 21 patients with localized PC and then compared PET/CT and MRSI findings with cancer aggressiveness factors, including biopsy GS, PSA, and PSA velocity.

They reported sensitivity and specificity of 80% and 29%, respectively for PET/CT and 89% and 29%, respectively for contrast-enhanced MRI in the diagnosis of PC. However, they showed no correlation between these functional imaging findings (11C-acetate PET/CT and MRI) and aggressiveness of PC.[14]

Several investigators have attempted to determine the ability of MRI and MRSI in predicting tumor staging and aggressiveness of PC.[3,6,14-17] In one study, authors presented an accuracy of 80% for MRSI in detecting the PC stage. Furthermore, they reported an AUC of 0.75 (confidence interval 95%) with the use of MRSI in detecting extraprostatic disease (EPD).[15]

Wang et al.[3] assessed the relationship between metabolite ratio and tumor proliferation using 1H-MRSI in PC. They found that the ratio of choline and creatine to citrate of PC was higher than that of the peripheral zone and benign prostate hyperplasia (BPH) and this estimated ratio of PC positively correlated with tumor cellularity. Finally, they concluded that MRSI is a useful modality in the prediction of the proliferative rate in the cancer tissue of the prostate gland.

In another study, Kobus et al.[6] offered MRSI for the evaluation of the aggressiveness of PC according to different metabolite ratios. They showed a relation between maximum Cho+Cr/Cit and PC aggressiveness (according to GS of the radical prostatectomy Specimen) among 43 patients with biopsy-proven PC.

A number of researchers have reported interobserver variability between radiologists in the interpretation of MRSI with respect to EPD.[15-17]

Mullerad et al.[17] mentioned that MRSI performed by experienced genitourinary radiologists may be used as a useful modality for the detection of ECE in PC.

Yu et al.[16] determined the ability of MRSI and endorectal MRI in the prediction of ECE of PC among 53 cases between less and more experienced radiologists. Overall, they noticed an AUC of 0.75 and 0.86 for less and more experienced readers in predicting ECE, respectively.

Table 4 presents the results of our study and other investigations in the evaluation of various imaging modalities for the prediction of EPD.

In our study, one reader reported all imaging, and prior to this study, he had an experience in reporting more than 300 MRSI. However, the AUC was less than that in other studies. More experience is required to reach a more accurate interpretation of the AUC. Moreover, other possible factors may affect this conclusion. Despite a relatively low AUC in our study in comparison to the literature, MRSI was associated with a significant predictive value (p value=0.001) in detecting EPD. Our study, similar to other investigations using MRSI, presents high specificity in predicting EPD.[15-17] In addition to MRSI findings, several EPD predictor factors are explained in the literature.[17] In our study, all evaluated variables except patient's age are associated with the prediction of EPD. Among these predictors, cancer-positive core percentages at biopsy and GS at biopsy have a larger AUC in comparison to the MRSI findings. There are several limitations to the present study. First, we used only one radiologist in setting of the MRSI interpretation. Using more numbers of radiologists to interpret the images would exclude bias arising from an observer variation.

Second, in this study, we evaluated predicting values of the combination of conventional MRI and MRSI in detecting PC ECE. Consequently, accuracy of conventional MRI only in diagnosing ECE and the usefulness or uselessness of adding MRSI is not assessed in current study.

Table 4. Review of the literature describing the accuracy of various imaging modalities in detecting locally advanced prostate cancer

Imaging modality	Author	No. of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
TRUS	Rifkin et al.[10]	230	66	46	63	49	-
Endorectal 3T MRI	Bloch et al.[13]	108					
	All readers		75	92	79	91	0.86
	Experienced readers		64	95	77	92	0.80
	Less experienced readers		83	88	80	90	0.91
MRSI	Mullerad et al.[17]		-	-	-	-	
(1.5T)	Genitourinary radiologist	163					0.833
	General body radiologist	181					0.646
	Yu et al.[16]	53					
	More experienced reader		54	96	81	88	0.86
	Less experienced reader		46	93	65	85	0.75
	Zhang et al.[15]	158	-	-	-	-	
	Reader 1						0.75
	Reader 2						0.74

TRUS: Trans-rectal ultrasound; MRI: magnetic resonance imaging; MRSI: magnetic resonance spectroscopy imaging; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve

In conclusion, adding MRSI to conventional MRI may be considered as a complementary diagnostic modality with high specificity and relatively low sensitivity in predicting locally advanced PC. Combination of this modality with other predictive factors helps the surgeon, oncologist, and patient to select appropriate treatment strategies.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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