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Evaluation of the Sensitivity of Multi-Parametric Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer among PSA Grey Zone Patients

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Abstract: The patients with prostatic specific antigen "PSA" (4-10ng/ml) are considered the grey zone patients. PSA level, either total or free to total, is used to screen or diagnose patients with prostate cancer. PSA is an organ specific marker not a disease specific test so it might show many false positive results resulting in un-necessary trans-rectal ultrasound(TRUS) guided biopsies. The multi-parametric magnetic resonance imaging(MP-MRI) is showing a good sensitivity in prostate cancer diagnosis. Eighty patients were enrolled in this study after assessment of their eligibility. Their PSA level ranged from (4.3-10 ng/ml) with free / total percentage >22%. All patients underwent either single or repeated TRUS guided biopsy in addition to multi-parametric MRI. Results revealed that the total PSA ranged from 4.3 to 10ng/ml and the free to Total PSA ranged from 9% to 19%. The prostate imaging reporting and data system(PIRADS) 1cases were 14, PIRADS 2 were 12, PIRADS 4were 24 and PIRADS 5 were 30. The MP-MRI negative cases were 26 while TRUS biopsy confirmed 22 negative cases and 4 cases were confirmed positive. The MP-MRI positive cases were 54 while the TRUS biopsy confirmed 50positive cases and 4 cases were negative. The sensitivity of theMP-MRI was 92.6%, the specificity was 84.6%, the positive predictive value was 92.6 %, the negative predictive value was 84.6 and the accuracy was 90%.o In conclusion: The MP-MRI demonstrated good sensitivity in detecting the PSA grey zone prostate cancerthatcould lead to limiting un-necessary TRUS biopsies.

Key words: Grey Zone PSA · Multi-Parametric MRI · TRUS Biopsy · Cancer Prostate

INTRODUCTION

Prostate cancer is considered a heterogeneous disease that has got a variable clinical significant behavior with progression from early to late stages [1, 2]. Up to the moment, there is no definite single therapeutic option for advanced prostate cancer, hence the identification of high risk individuals and the early detection of the local tumor are highly recommended [3]. Diagnosis of prostate cancer traditionally depends on some tools such as digital rectal examination, serum prostate specific antigen (PSA) and trans-rectal ultrasound (TRUS) guided biopsy [4]. Screening of prostate cancer with the widespread use of PSA might help in the detection of early and small prostate lesions. Serum PSA level is considered the most accepted marker to detect this type of cancer. Generally, PSA is an organ specific marker but not a disease specific test, therefore; its use for prostate cancer screening does not have the perfect sensitivity according to several studies [5]. Accordingly, its false-positive screening results might subject many patients to un-necessary TRUS guided prostatic biopsy which is an invasive procedure having a considerable co-morbidity and even mortality [5], however, TRUS biopsy is still the most reliable diagnostic measure to confirm presence of malignant prostatic tissue [6].Multi-parametric magnetic resonance imaging (MP-MRI) nowadays is showing increasing frequency in the prostate cancer diagnosis. It has a role in detection and localization of the disease. This helps in tuning the decision as regards the indication, type and site of a prostate biopsy in order to confirm cancer diagnosis. Furthermore, MP-MRI has the

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ability to give information about the characteristics and aggressiveness of the detected cancer including tumor progression with time [7, 8]. The growing evidences concerning the ability of MP-MRI to identify prostate cancer has raised the tendency towards employing TRUS guidedbiopsy [9]. MP-MRI combines two forms; the diffusion weighted imaging (DWI) and the dynamic contrasted enhanced (DCE) so as to have functional images allowing great value in distinguishing malignant from benign prostate tissue[10]. Concerning the PSA grey zone, there are still some studies that have controversy in determining the Grey zone PSA cut-off and the optimum investigation plan for it but the total PSA range (4-10 ng/ml) is still quite acceptable for the term grey zone PSA [11].

MATERIALS AND METHODS

Study Design: This cross sectional study was held between September 2017 and March 2020. The patients were recruited from the urology department and clinic at Ain-Shams University while the MP-MRI was performed in a private center in Cairo. The study was approved by the research ethics committee(REC) of Ain-Shams University (FWA 000017585, approval number MD284/2017, the chair of REC professor Fathy Tash). An informed signed consent was obtained from all patients.

Confidentiality: All research discussions with patients were conducted in a closed room in the outpatient clinic. We ensured that no one other than the investigators were present in the room during the study.

Declaration of Interests: No interest other than the information gained and data obtained from participants for the research study.

Data Availability: The data associated with this study are confidential and only available via the corresponding author upon reasonable request.

Ancillary and Post-Trial Care: The study does not involve any physical, psychological or social risks. The study could be stopped if any unexpected complaints were reported by the patients during the study.

Dissemination Policy: Reports and results were sent by email to each participant individually andcopy of MP-MRI and TRUS-guided biopsy given to all patients.

Participants: The study included 90 patients, 10 of them were excluded so the final number of patients was 80. The criteria of selection were a total PSA level of (4 ng/ml-10ng/ml) with free/ total percentage< 22% after exclusion of prostate infection with or without abnormal digital rectal examination (DRE), Negative single TRUS biopsy with total PSA (4 ng/ml-10ng/ml) prior to the MP-MRI, All patients were evaluated with full history and clinical examination and emphasis on the history of the present illness as regards onset, course and duration of any irritative symptoms such as frequency, nocturia or dysuria in addition to obstructive symptoms like decreased force of urination, hesitancy, intermittency, post-voiding dribbling or straining, past history of any associated medical condition and any other similar condition among the family members. Patients were examined generally and digital rectal examination (DRE) was performed for all patients. All patients were investigated for urine analysis, complete blood picture, bleeding time, clotting time, PSA (total and free), pelvi-abdominal ultrasonography and MP-MRI.

Magnetic Resonance Imaging (MRI) Protocol: MRI was performed on a 3-T MRI system (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany) with an 18-element body phased array coil and a 32-element spine array coil. Before the contrast injection, anatomical MRI was performed including sagittal, oblique, axial and coronal T2-WI HASTE (half-Fourier acquisition single-shot turbo spin-echo) on the prostate without fat-suppression (FS), DWI was performed using a single-shot echo-planar imaging (EPI) pulse sequence during free breathing. Parallel imaging technique was used to reduce the echo train length. 3D diagonal encoding was performed using monopolar gradients with the following b-value(s):0, 800 and 1400 sec/mm^2. Gadolinium-based contrast was given intravenously by means of a power injector (Ulrich Medical® EP MR, MEDRAD Inc., Indianola, IA, USA), at an infusion rate of 1 ml/s. Then, axial T1-weighted TWIST dynamic imaging obtaining 40 frames in 2 minutes. It is free-breathing technique without fat suppression, the reports of the MP-MRI were composed and revised by an expert radiologist (approximately performing 400 ± 10% MP-MRI of the prostate per year).

TRUS Biopsy Protocol: TRUS biopsy was done by an experienced intervention radiologists(performing yearly around 500 TRUS biopsies) using 12 core scheme of prostatic biopsy in addition to a biopsy from any lesion

determined by the MP-MRI.The specimens were examined by one of the most experienced pathologists who performs thousands of tumor specimen examinations per year in Egypt and the data were collected and analyzed.

Statistical Analysis: All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) &Med Calc 13 for windows (Med Calc Software bvba, Ostend, Belgium). Continuous data are expressed as the mean ± SD & median (range) and the categorical data are expressed as a number (percentage).

Continuous variables were checked for normality by using Shapiro-Wilk test. Mann Whitney U test was used to compare two groups non-normally distributed variables. Kruskal Wallis H test was used to compare more than two groups non-normally distributed variables. Validity of multiparametric MRI in diagnosis of prostatic carcinoma was calculated using diagnostic performance depend on sample 2x2 contingency tables generation using TRUS biopsy as the reference . Sensitivity, specificity, positive predictive value, negative predicitive value, accuracy and their corresponding 95%Confidence interval were calculated.

All tests were two tailed. the p-value < 0.05 was considered statistically significant(S), the p-value < 0.001 was considered highly statistically significant (HS) and the p-value>0.05 was considered statistically insignificant (NS).

RESULTS

The age of patients included in this study ranged from 49 to 85 years with an average of 63.5 years. The main presentation of patients was dysuria with a percentage of 47.5% and the minor presentation was supra-pubic pain and weak stream with a percentage of 7.5% for each presentation. The total PSA ranged from 4.3 to 10 ng/ml with an average range of 7.85 while the free PSA to Total PSA ranged from 9% to 19% with an average range of 14.35. The number of cases with positive DRE findings was 26 cases with ratio of 32.5% which is an elevated percentage that might be due to the high age associated with lack of interest to undergo examination. As concerns the PIRADS score, the number of cases with PIRADS 1 was 14 cases, PIRADS 2 were 12 cases , PIRAD 4 were 24 cases and the number of PIRADS 5 cases was 30. The number of cases diagnosed as negative for prostate cancer by the MP-MRI was 26. The PIRADS scores 1 and 2 raise the possibility of benign prostate while the positive cases for cancer with PIRADS score 4 and 5 were 54 cases according to the MP- MRI. The number of patients diagnosed as benign cases by TRUS biopsy was 26 and the positive cases for cancer according to the TRUS biopsy were 54 cases as shown in Table 1. The cases with PIRADS 3 score were excluded from the study in order to prevent the overlapping between the suspected malignant and benign cases as PIRADS 3 is considered as a midway between benign and malignant situations.

According to the PIRADS score grading from 1 to 5, the increase in the score means an increase in cancer probability. The cases with PIRADS 1 were 14 with a range of total PSA 4.5-9.6 ng/ml, the cases with PIRADS 2 were 12 with a range of total PSA 5.9-10 ng/ml, the cases with PIRADS 4 were 24 with a range of total PSA 6-10 ng/ml and the cases with PIRADS 5 were 30 with a range of total PSA 4.3-10ng/ml. The P-value was not significant and according to the relation between PIRADS score and the free/total PSA percentage, the cases with PIRADS 1 hada range between 16.6 and 19 with an average of 17.7, the cases with PIRADS 2 had a range between 13.7 and 18.9 with an average of 18.45, the cases with PIRADS 4 had a range between 10.9 and 18.5 with an average of 13.75 and cases with PIRADS 5 ranged between 9 and 15.6 with an average of 12 with P-value less than 0.001 which is highly significant as emphasized in Table 2.

Upon comparing the accuracy of the MP-MRI regarding the total PSA and free/total PSA, the negative cases were 26 and the total PSA range was 4.5-10 ng/ml with a mean value of 7.75 while the positive cases were 54 with total PSA range of 4.30-10 ng/ml and a mean value of 7.7. It is then apparent that there was no significant difference in the mean PSA value among both negative and positive cases. Regarding the free/total PSA with the MP- MRI, the range of negative cases was 13.7-19 with a mean value of 17.54 and the range of the positive cases was 9-18.5 with a mean value of 13.65 showing highly significant difference between both situations as seen in table 3. Concerning the accuracy of the MP-MRI as regards confirming the data based on the TRUS biopsy, the negative cases were 26 cases with confirmation of 22 negative cases according to the TRUS biopsy while 4 cases had shown positive specimens. The positive cases by MP-MRI were 54 cases with confirmation of diagnosis by TRUS biopsy in 50 cases as shown in figure 1and figure 2 while4 cases had shown negative specimens for malignancy being just prostatic abscesses.

The sensitivity of the MP-MRI was 92.6%, the specificity was 84.6%, the positive predictive value was 92.6 %, the negative predictive value was 84.6 and the accuracy was 90% as illustrated in Table 4 and Table 5.

Table 1: Clinical and pathological characters of the studied cross-section

Basic charactertics	The studied cross-section(N=80)	
Age (years)		
Mean ± SD	65.72 ± 10.08	
Median (Range)	63.50 (49 – 85)	
Complaint	No.	%
Dysuria	38	47.5%
Hematuria	22	27.5%
Retention	8	10%
Weak stream	6	7.5%
Suprapubic pain	6	7.5%
Total PSA (ng/dl)		
Mean ± SD	7.66 ± 1.60	
Median (Range)	7.85 (4.30 – 10)	
Free PSA (ng/dl)		
Mean ± SD	1.12 ± 0.31	
Median (Range)	1.09 (0.50 – 1.85)	
Free PSA to Total PSA		
Mean ± SD	14.65 ± 2.80	
Median (Range)	14.35 (9 – 19)	
PR findings	No.	%
Negative	54	67.5%
Positive	26	32.5%
PIRADS	No.	%
PIRADS I	14	17.5%
PIRADS II	12	15%
PIRADS IV	24	30%
PIRADS V	30	37.5%
MRI diagnosis	No.	%
Negative	26	32.5%
Positive	54	67.5%
TRUS biopsy diagnosis	No.	%
Negative	26	32.5%
Positive	54	67.5%

N: number, SD: standard deviation, PR: rectal examination.

Table 2: Relation between PIRADS score and total PSA and free/total PSA

	PIRADS					
	PIRADS 1 (N=14)	PIRADS 2 (N=12)	PIRADS 4 (N=24)	PIRADS 5 (N=30)	Test_	p-value (Sig.)
			Total PSA (ng/ml)			
Mean ± SD	6.94±1.57	8.31±1.38	7.95±1.29	7.50±1.89	2.716	0.438 (NS)
Median (Range)	7.10 (4.50 – 9.60)	8.55 (5.90 – 10)	7.95 (6 – 10)	7.80 (4.30 – 10)		
			Free to total PSA			
Mean ± SD	17.55±0.84	17.53±2.01	13.85±2.34	12.80±1.94	20.405	<0.001
(HS) Median (Range)	17.70 (16.60 – 19)	18.45 (13.70 – 18.90)	13.75 (10.90 – 18.50)	13 (9 – 15.60)		

N: number, SD: standard deviation, P-value: probability value, NS: non-significant, HS: highly-significant

Table 3: Comparison between negative and positive MRI regarding total PSA and free to total PSA

	MRI			
	Negative (N=26)	Positive (N=54)	Test_	p-value (Sig.)
	Total PSA (ng/dl)			
Mean ± SD	7.57±1.59	7.70±1.64	-0.246	0.806
(NS) Median (Range)	7.80 (4.50 – 10)	7.90 (4.30 – 10)		
	Free to total PSA			
Mean ± SD	17.54±1.43	13.26±2.15	-4.420	<0.001
(HS) Median (Range)	17.80 (13.70 – 19)	13.13 (9 – 18.50)		

N: number, SD: standard deviation, P-value: probability value, NS: non-significant, HS: highly-significant

Table 4 & 5: Validity of multi-parametric MRI in diagnosis of prostate cancer

		Estimate	(95%CI)
SENSITIVITY (%)		92.6%	(75.7 – 99.1)
SPECIFICTY (%)		84.6%	(54.6 – 98.1)
POSITIVE PREDICTIVE VALUE (%)		92.6%	(77.7 – 97.8)
NEGATIVE PREDICTIVE VALUE (%)		84.6%	(58.7 – 95.5)
ACCURACY (%)		90%	(76.4 – 97.2)
		TRUS biopsy	
		Positive	Negative
Multi-parametric MRI	Positive (54)	50	4
	Negative (26)	4	22
Total (80)		54	26

DISCUSSION

This study is considered one of the first studies held in Egypt concerning the accuracy of the MP-MRI of the prostate. The study was limited to the grey zone PSA patients which has got limited publications all over the world.The number of patients was also limited because the selection was limited only to the grey zone patients in addition to the fact that the prostate cancer rate in theMiddle East is lower than that in other world countries. The study has considered the choice of the optimum reliable procedures to ensure the best possible accuracy of prostate cancer detection. The comparison of this with other closest similar studies such as those done by Wroclawski *et al*. [12], Ahmed *et al*. [13] and Haffner *et al*. [14], as concerns the number of patients included in the study, it was 80 patients in this study, 40 patients in Wroclawskia nd colleagues study, 576 patients in Ahmed's team study and 555 patients in Haffner's team research work. In another aspect, this study performed MP-MRI using 3 Tesla machine while Wroclawski's team used 1.5 Tesla machine, Ahmed and partners used the 1.5 Tesla machine and Haffner with his associates also used the 1.5 Tesla machine for all patients before TRUS biopsy. This study included patients with PSA (4-10 ng/ml) with free to total percentage less than 22% while Wroclawski's team study included patients with PSA more than 4 ng/ml or more than 2 ng/ml employing 5-alpha-reductase inhibitor, Ahmed and his research investigators included patients with elevated PSA up to 15 ng/ml while Haffner and co-researchers included patients with elevated PSA more than 4 ng/ml. This study used the extended TRUS biopsy scheme (12 core biopsies)while Wroclawski's team used TRUS-guided systematic 14-core biopsies (six from each lobe and one more from each transitional zone). Heffner's team study used also the extended core biopsy (8-14 core biopsies) while Ahmed's associates study used template prostate mapping biopsy (TPM-biopsy) combined with the ordinary 10-12 core TRUS biopsy. It was found in this study that the sensitivity of MP-MRI is 92.6% (75.7%-99.1%), Wroclawski's team found it 75%, Ahmed'sstudy group has found that the sensitivity of MP-MRI 93% (88%-96%)while Haffner's and investigators found that the sensitivity is 95% (92%-97%).It was found in this study that the positive predictive value of MP-MRI is 92.6% (77%-97.8%) and Wroclawski's group found it 75% while Ahmed and co-workers found this value 51% (46%-%56). The specificity of MP-MRI was found in this study84.6 % (54.6%-98.1%), Wroclawski's team has found it 93 % and Ahmed's research group study has found the specificity 41% (36-46) while Haffner's and partners found it 83% (78%-87%). This study has found the negative predictive value of MP-MRI 84.6% (58.7-95.5)while Wroclawski's team found it93.8 %and Ahmed team has found it 89% (83%-94%).

CONCLUSION

MP-MRI showed good sensitivity in detecting lesions among grey zone PSA patients. Hence, it could help in avoiding un-necessary TRUS biopsies and help also in targeting the lesion with less number of biopsies. Further studies are necessary to validate the strategy of using the MP-MRI in the management of grey zone prostate cancer patients.

REFERENCES

1. Baca, S.C. and L.A. Garraway, 2012. The genomic landscape of prostate cancer; Front Endocrinol., (Lausanne), 3: 69.
2. Nodouzi, V., M. Nowroozi, M. Hashemi, G. Javadi and R. Mahdian, 2015. Concurrent Down-Regulation of PTEN and NKX3.1Expression in Iranian Patients with Prostate Cancer, Brazilian Journal Urology, 41(5): 898.

3. Barentsz, J.O., J. Richenberg and R. Clements, 2012. European Society of Urogenital Radiology. ESUR prostate MR guidelines Eur. Radiol., 22: 746-757.
4. Noldus, J., M. Graefen, A. Haese, R.P. Henke, P. Hammerer and H. Huland, 2000. Stagemigrtion in clinically localized prostate cancer. Eur. Urol., 38: 74-78.
5. Wagenlehner, F.M., E.V. Oostrum, P. Tenke, Z. Tandogdu, M. Cek and M. Grabe, 2013. Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, aprospective multinational multicentre prostate biopsy study. Eur, Urol., 63: 521.
6. Baco, E., E. Rud, L. Magne Eri, G. Moen, L. Vlatkovic, A. Svindland, H.B. Eggesbo and O. Ukimura. A Randomized. 2016. Controlled Trial To Assess and Compare the Outcomes of Two-core Prostate Biopsy Guided by Fused Magnetic Resonance and Transrectal Ultrasound Images and Traditional 12-core Systematic Biopsy, European Urology, 69: 149-156.
7. Dickinson, L., H.U. Ahmed, C. Allen, J.O. Barentsz, B. Carey, J.J. Futterer, S.W. Heijmink, P. Hoskin, A.P. Kirkham, A.R. Padhani, R. Persad, P. Puech, S. Punwani, A. Sohaib, B. Tombal, A. Villers and M. Emberton, 2013. Scoring Systems Used for the Interpretation and Reporting of Multiparametric MRI for Prostate Cancer Detection, Localization and Characterization: Could Standardization Lead to Improved Utilization of Imaging Within the Diagnostic Pathway? Journal of Magnetic Resonance Imaging, 37: 48-58.
8. Alonzi, R., A.R. Padhani and C. Allen, 2007. Dynamic contrast enhanced MRIin prostate cancer. Eur. J. Radiol., 63: 335-350.
9. Moore, C.M., N.L. Robertson, N. Arsanious, T. Middleton, A. Villers, L. Klotz, S.S. Taneja and M. Emberton, 2013. Image-guided prostate biopsy using magnetic resonance imaging–derived targets: a systematic review. Eur. Urol., 63: 125-40.
10. Delongchamps, N.B., F. Beuvon, D. Eiss, T. Flam, N. Muradyan, M. Zerbib, M. Peyromaure and F. Cornud. Multiparametric, M.R.I., 2011. is helpful to predict tumor focality, stage and size in patients diagnosed with unilateral low-risk prostate cancer, Prostate Cancer and Prostatic Diseases, 14: 232-237.
11. Sönmez, G., T. Şevket, T. Ombul, T. Demirtaş, F. Öztürk and A. Demirtaş, 2019. A Comparative Study, 2019. Has MRI-guided Fusion Prostate Biopsy Changed the Prostate-specific Antigen Gray-zone Range?, Cureus, 11(12).
12. Wroclawski, M.L., P.P. Kayano, B.S. Amaral, G.C. Mariotti, F.I. Yamauchi, J.D. Cha, A. Carneiro, F. Korkes, A.S. Vitalli, T.C. Mussi, G.C. Lemos and R.H. Baroni, 2020. Can multiparametric magnetic resonance of the prostate avoid biopsies in patients with elevated PSA and surgical indication for benign prostatic enlargement?, Abdominal Radiology.
13. Ahmed, H.U., A.E. Bosaily, L.C. Brown, R. Gabe, R. Kaplan, M.K. Parmar, Y. Collaco-Moraes, K. Ward, R.G. Hindley, A. Freeman, A.P. Kirkham, R. Oldroyd, C. Parker and M. Emberton, 2013. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study, The Lancet.
14. Haffner, J., L. Lemaitre, P. Puech, G. Haber, X. Leroy, J.S. Jones and A. Villers 2011. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection, BJU international.