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RESEARCH ARTICLE

ASSESSMENT OF EFFICACY OF MULTI-PARAMETRIC MRI BY CORRELATION WITH GLEASON SCORING IN DETECTION OF CARCINOMA PROSTATE

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ABSTRACT

Objectives: To find out the efficacy of multi-parametric MRI as a noninvasive diagnostic investigation in carcinoma prostate and its correlation with Gleason scoring among men with PSA levels between 4 to 10 ng/ml and with normal digital rectal examination.
Methods: A prospective study was done in Institute of Urology, MMC, Chennai between September 2015 to April 2016. 25 male patients who presented with obstructive LUTS with PSA 4-10 ng/ml and a normal DRE were included in the study. Patients with active UTI, prostatitis, initial presentation as AUR, nodular prostate on DRE, claustrophobia or metal implants were excluded from study. All patients were subjected to 13 core TRUS guided biopsy and multi-parametricMRI.
Results: The age of the patients in the current study ranged from 51 to 81 years, with a mean age of 66.76 ± 7.8 years. 9 patients (36%) were positive for malignancy in multi-parametric MRI while 8 patients (32%) were positive for malignancy in TRUS biopsy. The multi-parametric MRI based PIRADS score had a sensitivity of around 100% and a specificity of 94.12% compared to the TRUS biopsy. According to the classification of multi-parametric-MRI based PIRADS score, about 24% of the patients had highly suspicious malignancy and about 12% had a probably malignant lesion while 16% of the patients had indeterminate lesions. There was also a positive linear correlation between PIRADS score & Gleason score and also PIRADS score &PSA levels.
Conclusion: Based on the findings of this study, it can be concluded that multi-parametric MRI of prostate for patients with grey zone PSA and normal DRE is an invaluable, non-invasive and feasible option to detect carcinoma prostate with a high sensitivity and specificity besides high predictive values and can help in identifying patients in need of biopsy. It can be also helpful in performing targeted biopsy and in characterizing the extent &aggressiveness of the prostate cancer.

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INTRODUCTION

Carcinoma of prostate is one of the leading causes of cancer death among aged men. It is the most common non-cutaneous cancer among men. The incidence of prostate cancer is on the rise primarily because of increased application of screening tests using prostate-specific antigen (PSA) and also partly because of the increase in life expectancy. Most of the prostate cancers are slow-growing and indolent rather than being aggressive and hence they seldom produce any symptoms until the advanced stage. Hence, early diagnosis of prostate cancer can lead to improved treatment outcomes besides aiding in the selection of multiple treatment options available.Traditionally, the methods employed include a prostate-specific antigen assay (PSA), Digital rectal examination (DRE) and Trans-rectal ultrasound guided biopsy (TRUS). The confirmatory diagnosis of prostate cancer can only be made by taking a biopsy which is usually a 12-core TRUS biopsy. However, all these methods have their own limitations and disadvantages. PSA assay levels lack sensitivity and specificity while the DRE is a crude technique with a low positive predictive value and high inter-observer variability. Studies have shown that TRUS biopsy can miss up to20% of prostate cancers because of under sampling of anterior prostate, apex and midline resulting in high false negativity. Moreover diagnosing carcinoma prostate in patients in grey zone of PSA [4 to 10 ng/ml] and patients with normal Digital rectal examination is still difficult. Also about 70% of initial biopsies performed in men with raised PSA levels are negative for prostate cancer hence increasing the burden of negative biopsies and increased screening costs.Because of these limitations of the currently existing techniques, the search for a diagnostic technique

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which is reliable, sensitive, specific with good positive and negative predictive values besides being non-invasive have led the researchers to consider radiologic imaging techniques like magnetic resonance imaging (MRI) as a diagnostic tool and especially multi-parametric MRI (mp-MRI) has received quite an attention in the recent years which builds upon the regular advantages of MRI. Multi-parametric MRI (mp-MRI) combines the anatomical imaging in T1 and T2 weighted images with the 2 functional methods like diffusion-weighted imaging (DWI), dynamic contrast enhanced imaging (DCE) with or without Magnetic resonance spectroscopy (MR spectroscopy). Besides aiding in the pre-biopsy diagnosis of cancer prostate, mp-MRI also helps in guiding biopsy either as real-time MRI-guided biopsy or a cognitive TRUS guided biopsy or fusion biopsy with MRI in combination with TRUS and also helps in characterizing the extent of the disease involvement which can aid in minimally-invasive procedures. Moreover it also helps in predicting the treatment outcomes and selecting amongst the various treatment options available.

Furthermore, diffusion-weighted imaging (DWI), dynamic contrast enhanced imaging (DCE) and Magnetic resonance spectroscopy shows promise in better characterization of the lesions and assessment of cancer aggressivenessin correlation with low, intermediate and high Gleason scores. Moreover, mp-MRI can bring down the number of negative biopsies among men with elevated levels of PSA and also can aid in improved surgical margin rate which reduces the risk of recurrences of cancer and thereby obviating the need for adjuvant radiotherapy.

The only major limitation of mp-MRI is the cost and availability but considering the potential advantages of mp-MRI in reducing the number of biopsies and decreasing the treatment costs by improved treatment outcomes and reduction in number of recurrences, mp-MRI still promises to be better diagnostic tool for screening and detection of prostate cancer.Even today, the confirmatory diagnosis of prostate cancer lies in the histologic examination performed on a biopsy specimen and application of Gleason scoring for grading of the two most common patterns of the cells from 1 (lowest) to 5 (highest) and adding them to yield a score with a maximum of 10 and scores above 7 are considered adverse towards prostate cancer. With this backdrop, this study was planned to assess the efficacy of multi-parametric MRI in detection of prostate cancer in correlation with Gleason scores of the biopsies among the men with prostate-specific antigen (PSA) levels between 4 to 10 ng/ml and with a normal digital rectal examination.

MATERIALS AND METHODS

This study was done prospectively at our institute for a period of from September 2015 to April2016. Ethical clearance was taken from the Institute Ethics Committee prior to the start of the study. 25 male patients who presented with obstructive LUTS with PSA 4-10 ng/ml and a normal DRE were included in the study. Patients with active UTI, prostatitis, initial presentation as AUR, nodular prostate on DRE, claustrophobia or metal implants were excluded from study.

The PI-RADS scoring is as follows

Score	Criteria	
A1	**T2WI for peripheral Zone**	
1	Uniform high intensity signal (SI)	
2	Linear, wedge shaped or geographic areas of lower signal intensity but not well demarcated	
3	Intermediate but not in categories 1 or 2 and 4 or 5	
4	Discrete and homogenous low intensity signal focus or mass confined to prostate	
5	Discrete and homogenous low intensity signal focus or mass not confined to prostate with extra-capsular extension or broad (1.5cm) contact with surface	
A2	**T2WI for Transition Zone**	
1	Heterogeneous adenoma with well-defined margins: organized chaos	
2	More homogenous areas of low signal but well-marginated	
3	Intermediate but not in categories 1 or 2 and 4 or 5	
4	Areas of more homogenous low signal intensity but ill-defined: erased charcoal sign	
5	Same as 4 + involvement of anterior fibromuscularstroma or anterior horn of PZ	
B	**Diffusion Weighted imaging (DWI)**	
1	No reduction in ADC and no increase in signal intensity in any high value *b* image (>b800)	
2	Diffuse, hyper-SI on >b800 image with low ADC but no focal features but linear, triangular or geographical features are allowed	
3	Intermediate but not in categories 1 or 2 and 4 or 5	
4	Focal areas of reduced ADC but iso-intense signal on high value *b* image (>b800)	
5	Focal areas/mass of reduced ADC but hyper-intense signal on high value *b* image (>b800)	
C	**Dynamic contrast enhanced MRI (DCE)**	
1	Type 1 enhancement curve	
2	Type 2 enhancement curve	
3	Type 3 enhancement curve	
+1	Focal enhancing lesion with curve type 2 or 3	
+1	Asymmetric lesion or lesion at unusual location with curve type 2 or 3	
D1	**Quantitative MRS - Choline+ Creatine/citrate ratios**	
Rating	**Peripheral zone**	**Transition zone**
1	<0.44	<0.52
2	0.44 – 0.58	0.52 – 0.66
3	0.58 – 0.72	0.66 – 0.80
4	0.72 - 0.86	0.80 – 0.94
5	>0.86	>0.94
D2	**Qualitative MRSI - For adjacent 3 voxels: Pattern analysis**	
1	Citrate peak height exceeds choline peak height >2 times	
2	Citrate peak height exceeds choline peak height >1 but <2 times	
3	Citrate peak height equals choline peak height	
4	Choline peak height exceeds Citrate peak height >1 but <2 times	
5	Choline peak height exceeds Citrate peak height >2 times	

All the 25 patients were subjected for 13-core TRUS guided prostate biopsy andmulti-parametric MRI.

Multi-parametric MRI

Multi-parametric MRIsequences included T1 and T2 weighted anatomical imaging, functional imaging using diffusion weighted MRI and DCE along with MR spectroscopy. The machine used in this study is SEIMENS 3.0 Tesla with phased array body coil. Multi-parametric MR imaging protocol included 2D T2w-MRI, DW-MRI, DCE-MRI and MRSI. High resolution Axial, Sagittal and coronal T2WI using T2w turbo spin echo sequence was taken in three orthogonal planes. The signal intensities of prostate gland involving lateral lobes, median lobe and periurethral glandular region were analyzed.T1 Axial and a 3D CSI MRS technique were also used.The prostate imaging- reporting and data system (PI-RADS) was followed in the study. The PI-RADS scoring is based on the European Society for Urogenital Radiology (ESUR) guidelines for uniform structured scoring system for components of multi-parametric MRI.The PI-RADS scoring system is basically a 5-point Likert scale system of scoring each individual lesion in each component of multi-parametric MRI and the total composite score out of 20 involving all 4 components like T2w-MRI, DWI-MRI, DCE-MRI and MR spectroscopy was calculated to classify the risk of malignancy for the lesion.

Total maximum score: 20 (T2W + DWI + DCE + MRS). Total minimum score: 4.This total score is the PI-RADS score which is interpreted as follows:

PI-RADS classification	Definition	Total score with T2W + DWI + DCE + MRS
1	Most probably benign	4 or 5
2	probably benign	6 – 8
3	Indeterminate	9 – 12
4	probably malignant	13 – 16
5	Highly suspicious of malignancy	17 – 20

This Total aggregate score of PI-RADS in the study was calculated and was correlated with Gleason score after the tissue biopsy.

TRUS scan and TRUS guided biopsy

All the twenty five patients were subjected for TRUS scan with 7 MhzAloka machine with rectal probe in left lateral position. Complete zonal anatomy of prostate was studied and systematic sextant biopsies of 13 core were taken. Each biopsy specimen was specifically labeled according to the orientation of biopsy site and sent for histopathological examination. All the patients were given one dose of ciprofloxacin 500 mg half an hour prior to TRUS biopsy. All the patients were given low rectal enema prior to biopsy. No patient developed any untoward complication following the procedure.

Statistical Analysis

Statistical analysis was done with SPSS software version 17.

RESULTS

The age of the patients in the current study ranged from 51 to 81 years, with a mean age of 66.76 ± 7.8 years. 9 patients (36%) were positive for malignancy in multi-parametric MRI while 8 patients (32%) were positive for malignancy in TRUS biopsy. The distribution of gleason score for patients positive for malignancy in TRUS biopsy were as follows.

Table 1. Distribution of Gleason Score for malignancies in TRUS biopsy

Gleason Score	Frequency	Percentage
8	3	37.5%
7	3	37.5%
6	2	25%
Total	8	100%

On evaluation of parameters of multi-parametric MRI like sensitivity, specificity, positive predictive value, negative predictive value, accuracy, the following results were obtained.

Table 2. Evaluation of mp-MRI against TRUS biopsy

Parameter	Value	95% CI
Sensitivity	100%	63.06% to 100%
Specificity	94.12%	71.31% to 99.85%
Positive Predictive Value	88.89%	51.75% to 99.72%
Negative Predictive Value	100%	79.41% to 100%
Accuracy	96%	73.21% to 100%

On classification of mp-MRI PIRADS score from high suspicion of malignancy to most probably benign, the following results were obtained.

Table 3. Classification of mp-MRI PIRADS score

PIRADS score	Frequency	Percentage
Highly Suspicious of malignancy	6	24.0
Probably Malignant	3	12.0
Indeterminate	4	16.0
Probably Benign	9	36.0
Most Probably Benign	3	12.0
Total	25	100.0

On correlation of mp-MRI PIRADS score with age, gleason score and PSA the following results were obtained.

Table 4. Correlation of mp-MRI PIRADS score with other variables

Variable	N	Correlation coefficient	p value
PIRADS score versus Age	25	-0.480	0.270
PIRADS score versus Gleason score	8	0.383	0.349
PIRADS score versus PSA	25	0.556	0.004

On comparison of mp-MRI variables between benign and malignant lesions on TRUS biopsy the following results were obtained.

Table 5. Comparison of mp-MRI variables between benign and malignant lesions on TRUS biopsy

Variable	Carcinoma Mean (± S.D)	BPH Mean (± S.D)	p value
Choline-creatine /citrate ratio	1.5875 (± 0.188)	0.6953 (±0.213)	<0.001
ADC value	1.0013 (±0.103)	1.7706 (±0.307)	<0.001
Total PIRADS score	18.25 (± 2.121)	7.59 (±2.210)	<0.001

DISCUSSION

As we can see from the results, 9 patients (36%) were positive for malignancy in multi-parametric MRI while 8 patients (32%) were positive for malignancy in TRUS biopsy. In our study mp-MRI shows slightly high efficacy in detecting malignancy in patients with gray zone PSA level and a normal DRE as compared to TRUS biopsy. The gleason score pattern in those patients diagnosed with malignancy on biopsy shows that higher the score, the chances of detecting cancer on mp-MRI also increases. (Table-1) The multi-parametric MRI based PIRADS score had a sensitivity of around 100 and a specificity of 94.12% compared to the TRUS biopsy (Table-2). Because of the sensitivity of the multi-parametric MRI being on the higher side, it can be said that multi-parametric MRI is an ideal screening tool for those patients especially in the grey zone between PSA 4 to 10ng/ml and based on the PIRADS scoring obtained by the patients in this group, TRUS biopsy can be applied for those with higher PIRADS scoring in the multi-parametric MRI. Also specificity of multi-parametric MRI is also on the higher side indicating its potential in eliminating the patients who would otherwise undergo TRUS biopsy for a negative result. Therefore, unwanted and unnecessary biopsies can be avoided using multi-parametric MRI and hence reducing the patient discomfort and unnecessary burden on the health system. Moreover the positive predictive valuewas 88.89% while the negative predictive value was 100%. The high negative predictivevalue of multi-parametric MRI indicates its capability of excluding patients with PSA levels between 4 and 10ng/ml for TRUS biopsy accurately. Hence the post-test probability of a patient with negative results in multi-parametric MRI to have a malignant lesion is literally zero.Theaccuracy of a diagnostic test, in this case multi-parametric MRI is the ability of the test to correctly diagnose those with disease and exclude those without the disease. The accuracy of multi-parametric MRI was 96%. Hence the role of multi-parametric MRI in patients especially within the grey zone between PSA 4 to10 ng/ml in deciding whether to go for TRUS biopsy is significant.According to the classification of multi-parametric-MRI based PIRADS score, about 24% of the patients had highly suspicious malignancy and about 12% had a probably malignant lesion while 16% of the patients had indeterminate lesions. All the remaining patients had benign lesions. The problem lies with these indeterminate lesions as definitive diagnosis cannot be made even with TRUS biopsy without surgical resection of prostate. (Table-3)There was a positive linear correlation between PIRADS score and Gleason score and also PIRADS score and PSA levels i.e. increase in levels of PIRADS score is associated with a corresponding increase in levels of Gleason score and in PSA levels (Table-4).Although the positive linear correlation between PIRADS score and Gleason score was not statistically significant, it indicates that among the patients who tested positive for malignancy in TRUS biopsy, the higher the Gleason sum score the higher the PIRADS score and hence role of multi-parametric MRI in characterizing the extent and aggressiveness of the malignancy is revealed.

This is an added advantage especially in cases of pre-biopsy MRI as it may help in targeted biopsy and also targeted therapy which limits the recurrence and also provides better guidance for complete surgical clearance. On the other hand, positive linear correlation between PIRADS score and PSA levels was statistically significant ($p<0.05$), it indicates that even among the patients within the grey zone between PSA 4 to 10ng/ml, the higher the PSA levels, the higher the PIRADS score and higher the risk of malignancy although the optimum cut-off for PSA levels cannot be determined.The mean choline-creatine/citrate ratio among the patients with TRUS diagnosed malignancy was higher {1.5875 (± 0.188)} in comparison to those with a negative TRUS biopsy {0.6953 (±0.213)} and this difference was statistically significant ($p<0.001$). The mean ADC value among the patients with TRUS diagnosed malignancy was lower {1.0013 (±0.103)} than those with a negative TRUS biopsy {1.7706 (±0.307)} and this difference was also statistically significant ($p<0.001$). (Table-5)The mean total PIRADS score among patients with a positive TRUS biopsy was 18.25 (± 2.121) while the mean PIRADS score among patients with a negative TRUS biopsy was only 7.59 (±2.210) which is almost 10 units lower showing the clear delineation between malignant lesions and the benign lesions.Studies have shown that because of the low predictive value of TRUS it is not recommended as a first-line screening test for early prostate cancer. A number of studies have confirmed the inability of TRUS to localize early prostate cancer. So to avoid unnecessary TRUS biopsies and at the same time detecting carcinoma in patients with grey zone PSA is a challenging task.Many studies have shown that the TRUS biopsies are limited by a low sensitivity of 60%, a PPV of only 25% and false-negative rate estimated to be as high as 15–34%. Combining MRI with TRUS-guided biopsy could help in (i) directing biopsy to the suspicious area and therefore improve its detection rate, and (ii) avoiding the biopsy in those who have no suspicious lesions and therefore avoiding all risks associated with an invasive biopsy.The research studies prospectively evaluating the role of MRI in men with a PSA level of < 10 ng/mL, who have poorest cancer detection rate and the highest false-negative rate on TRUS biopsy found a cancer detection rate about three times better, and a NPV approaching 100%. Similar negative predictive value was obtained in this study also.

This study findings are similar to Delongchamps NB *et al*[18] were the tumor size was correctly estimated in 77% of cases and about 80% of the bilateral cancers were detected and also multi-parametric MRI can be used to rule out bilateral involvement and also of very good prognostic value.Similar findings were observed by de Rooij M *et al*[19]in a meta-analysis of studies for the accuracy of multi-parametric MRI which showed a specificity of 88% and a sensitivity of 74% for multi-parametric MRI in prostate cancer detection. Moreover the negative predictive value was in the ranged from 66% to 81% in the above stated study.The sensitivity and specificity of multi-parametric MRI observed in this study was higher than that of one observed by Citak*et al.*(2014)as they tried to predict the final Gleason score based on the pre-operative multi-parametric MRI (3 Tesla) using the linear discriminant analysis (LDA) and support vector machine (SVM). Using a standard principal component analysis before Gleason classification, the sensitivity was 51.19% and 64.37% with specificities of 72.7% and 39.9% for LDA and SVM, respectively. They concluded that the SVM classifier resulted in a slightly higher sensitivity but low specificity than LDA. Mowatt *et al*. (2013) did a systematic review and an economic evaluation on the diagnostic accuracy and cost-effectiveness of MR spectroscopy (MRSI) and enhanced MRI techniques (DCE and DWI) for localizing the prostate abnormalities for biopsy. They observed that sensitivity was highest for MRSI at 92% while TRUS imaging had a high specificity of 81%. Similar results of high sensitivity and specificity was observed in the

current study. They concluded that MRSI had high sensitivity and specificity than the T2-MRI.If MRSI &DWI show high sensitivity for detection of moderate to high risk patients and also at the same time negates patients with no or low risk of cancer towards undergoing biopsy, then in that case these imaging techniques will be cost-effective.Based on these study findings, it can be safely said that multi-parametric MRI has high sensitivity and specificity with better predictive values and hence pre-biopsy multi-parametric MRI can serve as not only as a screening tool but also a valuable diagnostic investigation providing assistance for guided and targeted biopsy besides having the ability to characterize the extent and aggressiveness of the prostate cancer at the earliest that too non-invasively.Moreover, application of multi-parametric MRI at least to the individuals with PSA levels in the grey zone between 4 to 10 ng/ml with a normal DRE can lead to reduction in number of negative biopsies and thereby reducing patient discomfort and unwanted expenditure. It can be concluded that multi-parametric MRI can play a significant role not only in screening for prostate cancer but also in the diagnosis, treatment and in the prognostic front.

Conclusion

Based on the findings of this study, it can be concluded that multi-parametric MRI of prostate for patients with grey zone PSA and normal DRE is an invaluable, non-invasive and feasible option to detect carcinoma prostate with a high sensitivity and specificity besides high predictive values and can help in identifying patients in need of biopsy and also helps in targeted biopsy and characterizing the extent and aggressiveness of the prostate cancer.

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