Section: Miscellaneous

Original Research Article

IMPROVING PROSTATE CANCER DETECTION IN THE PSA GRAY ZONE: A STUDY ON THE EFFICACY OF MULTIPARAMETRIC MRI

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ABSTRACT

Background: To evaluate the efficacy of T2-weighted imaging, dynamic contrast-enhanced MRI (DCE-MRI), and diffusion-weighted imaging (DWI) for detecting prostate cancer in patients with total serum prostate-specific antigen (PSA) levels of 4–10 ng/mL, which is referred to as the "gray zone.

Material and Methods: This prospective study included a total of 108 patients with lower urinary tract symptoms (LUTS) and serum PSA between 4 and 10 ng/mL, without abnormal digital rectal examination (DRE) findings of prostate. PIRADS score (V2) was calculated using multi-parametric magnetic resonance imaging (mp-MRI) before TRUS biopsy of prostate. Relationships among PIRADS score, PSA& presence of carcinoma prostate in TRUS biopsy were statistically analyzed.

Results: Mp MRI had a sensitivity and specificity of 100% and 84.59 % respectively for overall cancer detection. Whereas, the sensitivity was 100% for clinically significant prostate cancers. The negative and positive predictive values were 85.89% and 78.57%% respectively for overall cancer detection whereas the negative predictive value (NPV) was 72.37 % for clinically significant cancer.

Conclusion: Combined T2-weighted imaging, DWI, and DCE-MRI findings appearto be potentially useful for detecting and managing prostate cancer, even for patients with gray-zone PSA levels. Our result shows that use of MpMRI could have avoided 67.59 % of unnecessary biopsies without missing any of cancers.

Keywords: Prostate Cancer, Biopsy, PSA, MpMRI, PI-RADS version.

INTRODUCTION

Carcinoma of the prostate ranks as the second most prevalent cancer among men globally and stands as a major contributor to cancer-related mortality.[1] Prostate-specific antigen (PSA) serves as a critical biomarker for the detection, staging, and monitoring of prostate cancer.[2] Although the risk of prostate cancer escalates with rising PSA levels, no PSA threshold entirely negates the risk. Notably, the Prostate Cancer Prevention Trial revealed that 15% of men with a PSA level of 4.0 ng/mL or less, coupled with a normal rectal examination, harbored prostate cancer.[3] In the PSA range of 4 to 10 ng/mL, the malignancy prevalence varies between 30-35%, and it further increases to over 67% when PSA exceeds 10 ng/mL.[4]

Despite its high sensitivity for cancer detection, PSA lacks specificity, particularly within the gray zone of 4–10 ng/mL.[5] To enhance the diagnostic accuracy in this range, derivatives of PSA, such as free PSA, are employed to improve malignancy detection.

The integration of total PSA evaluations and rectal examinations does not guarantee absolute accuracy in malignancy detection; thus, biopsy remains the definitive standard for diagnosing prostate cancer. The ongoing quest for a non-invasive screening method continues, especially for cases in the gray

zone where many patients undergo unnecessary biopsies.

Recent advancements have positioned multiparametric MRI (MpMRI) as a pivotal tool for decision-making in the detection, staging, and treatment planning of prostate cancer.[7] It has also emerged as a valuable method for identifying clinically significant prostate cancer, particularly in patients with previous negative biopsy results.[8] The Prostate Imaging Reporting and Data System (PI-RADS) was initially established in 2012 to standardize MpMRI reporting, with the updated PI-RADS version 2 introduced in 2015.[9] Meta-analyses have demonstrated that version 2 significantly enhances diagnostic performance compared to its predecessor.[11]

To date, limited studies have explored the efficacy of MRI in patients with PSA levels within the gray zone.[10,11] In 2011, Tamada et al. reported a sensitivity and specificity of 83% and 80%, respectively, for a combination of T2-weighted, dynamic contrast-enhanced, and diffusion-weighted sequences in patients with PSA levels between 4-10 ng/mL.[11] However, these studies were conducted before the advent of the PI-RADS reporting system.

In light of the advantages offered by PI-RADS v2, we initiated this prospective study to evaluate the utility of MpMRI in gray zone cases for the detection of prostate cancer. Our aim is to assess whether combining PSA with MpMRI can enhance the detection rate of malignancy, potentially reducing the need for biopsy in this specific cohort of men. It is imperative to remember that, while prostate biopsy remains the gold standard for cancer detection, it is an invasive procedure associated with both minor and major complications.[12,13]

MATERIAL AND METHODS

Study Design and Setting: This prospective study was conducted at SMS Medical College and Hospital, Jaipur, from December 2018 to February 2020. The study protocol was approved by the institution's ethics committee.

Participants: Men aged 50–80 years, presenting with lower urinary tract symptoms and sonographically confirmed prostatomegaly (with no other abnormalities), normal digital rectal examinations, and total Prostate-Specific Antigen (PSA) levels between 4 and 10 ng/ml were considered for inclusion. Participants were required to undergo a repeat PSA test two weeks after the initial visit; those exhibiting a decrease in PSA by ≥ 1 ng/ml were excluded. Written informed consent was obtained from all participants.

Exclusion Criteria: Patients were excluded if they had evidence of urinary tract infections, palpable rectal abnormalities, prostatitis, urinary tract or catheterization within the past week, prostate weight exceeding 100 grams on sonography, recent use of 5α-reductase inhibitors, history of prostate surgery or biopsy within the last three months, bleeding disorders, deranged renal functions, metallic implants, or were unfit for MRI.

Imaging and Biopsy Procedures: Qualified patients underwent multiparametric MRI (MpMRI) using a 3 Tesla system, including T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging sequences. Prostate MRI assessments were conducted by an experienced radiologist with over seven years of experience, adhering to the Prostate Imaging Reporting and Data System version 2 (PI-RADS v2). Following MRI, all subjects underwent a transrectal ultrasound-guided (TRUS) 12-core systematic needle biopsy, with additional cores obtained from areas appearing suspicious. Antibiotic prophylaxis was administered to all patients undergoing biopsy.

Outcome Measures: The primary outcomes were PI-RADS scores and total PSA levels, compared against the results of the TRUS biopsy, which served as the gold standard for detecting malignancy. A PI-RADS score of ≥ 3 was considered indicative of cancer. Clinically significant prostate cancer was defined as having a Gleason score ≥ 7.

Statistical Analysis: Data analysis was performed using SPSS. The Chi-square test and ANOVA were employed for categorical and continuous variables, respectively. Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic performance of various parameters.

Study Flow: A total of 171 men were initially recruited based on PSA levels. Following the screening process, 115 eligible participants underwent total PSA estimation after excluding 56 men due to a drop in PSA levels. MpMRI was successfully performed in 114 cases, excluding one case due to a metallic femur implant. Out of these, 108 participants underwent TRUS-guided biopsy after accounting for dropouts and refusals.

RESULTS

In this prospective study, a total of 108 men successfully completed the evaluation aimed at exploring the diagnostic utility of multiparametric MRI (MpMRI) in detecting prostate carcinoma among men with gray zone PSA levels (4-10 ng/ml). The study's participant cohort primarily consisted of older adult men with a mean age of 66.28 years. The average prostate size reported was 48.71 grams, and the mean PSA level was 8.25 ng/ml.

The clinical outcomes revealed that 67.6% (73/108) of the participants were diagnosed with benign prostatic hyperplasia (BPH), while 32.4% (35/108) were diagnosed with prostate carcinoma. Within the group diagnosed with carcinoma, 11 cases (10.18% of the total cohort) were identified as having clinically significant prostate cancer. The breakdown of Gleason scores among these cases showed a distribution of 54.2% with a score of 3+3,

31.4% with a score of 7, and 14.2% with scores ranging from 8 to 10, indicating varying degrees of cancer aggressiveness.

MpMRI played a crucial role in this study, with PI-RADS categorization used to assess the MRI images. The distribution of PI-RADS scores was as follows: 44.4% (48/108) were categorized as PI-RADS 1, 24.1% (26/108) as PI-RADS 2, 13.9% (15/108) as PI-RADS 3, 9.3% (10/108) as PI-RADS 4, and 8.3% (9/108) as PI-RADS 5. This gradation reflects the suspected increasing likelihood of malignancy with higher PI-RADS scores.

The correlation analysis between PI-RADS categories and biopsy results was a critical component of the study. Although the correlation between PI-RADS categories and PSA levels showed a positive trend (r=0.12), it was statistically insignificant (p=0.20). However, a significant positive correlation was found between PI-RADS categories and TRUS biopsy outcomes (r=0.58, p<0.01), underscoring the potential of MpMRI in enhancing diagnostic precision.

To quantitatively assess the effectiveness of MpMRI, sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were calculated considering biopsy as the gold standard. MpMRI demonstrated a sensitivity of 100%, specificity of 84.59%, positive predictive value of 78.57%, negative predictive value of 85.89%, and an overall accuracy of 83.52%. These metrics affirm the robustness of MpMRI in detecting prostate cancer.

Furthermore, the receiver operator characteristic (ROC) curve analysis for MpMRI yielded an area under the curve (AUC) of 0.971 (95% CI .944-.998), highlighting its exceptional diagnostic performance in this clinical setting. This AUC value strongly suggests that MpMRI is a superior test for detecting prostate cancer among men with intermediate PSA levels, potentially guiding more accurate clinical decision-making and reducing unnecessary biopsies.

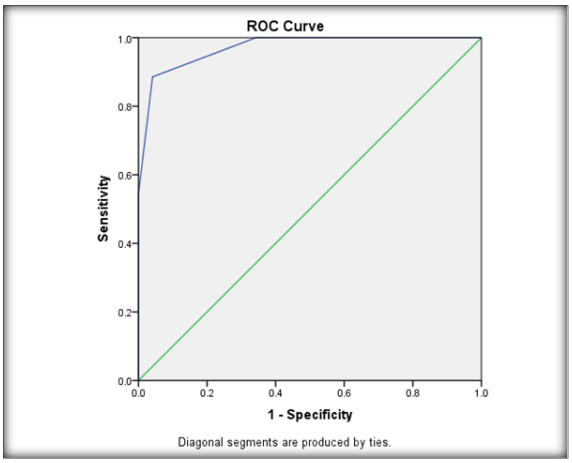

Figure 1: MRI overall cancer detection – ROC curve

Table 1: Characteristics of Study Population

Parameters	Value
Age (Mean±SD)	66.28±7.32
Prostate Size in gm (Mean±SD)	48.71±14.12
PSA (ng/ml)	8.25±1.39
A. Pirads Category	
Multiparametric MRI	
Pirads Category: 1, N (%)	48 (44.4)
Pirads Category: 2, N (%)	26 (24.1)
Pirads Category: 3, N (%)	15 (13.9)
Pirads Category: 4, N (%)	10 (9.3)
Pirads Category: 5, N (%)	9 (8.3)
Biopsy Report	
Benign, N (%)	73 (67.6)
Adenocarcinoma, N (%)	35 (32.4)
Gleason score 3+3 3+4 4+3 8 9	 19 05 06 03 02

Table 2: Association between Pirads Category with PSA and biopsy

Pirads Category	PSA		r value	p value
	Mean	SD		
1.00	8.01	1.48	0.12	0.20
2.00	8.04	1.35		
3.00	8.08	1.49		
4.00	8.21	1.24		
5.00	8.83	.81		
Total	8.25	1.39		
Anova Test	1.28			
p value	0.28			

Pirads Category	Benign		Adenocarcinoma		r value	p value
	N	%	N	%		
1.00	48	100	0	0	0.58	<0.01*

2.00	22	84.62	4	15.38		
3.00	3	20	12	80		
4.00	0	0	10	100		
5.00	0	0	9	100		
Chi Square	81.59					
p value	<0.01*					

Table 3: Sensitivity, specificity and accuracy of MpMRI in reference to prostatic biopsy

Parameters	Considering Biopsy as Gold Standard	Considering Clinically Significant Prostate Cancer as Gold Standard
Sensitivity	100%	100%
Specificity	84.59%	32.39
Positive Predictive Value	78.57%	24.68
Negative Predictive Value	85.89%	72.37
Accuracy	83.52%	46.48

Table 4: ?

Area Under the Curve				
Test Result Variable(s): PIRADS (V2) CATEGORY				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.971	.014	.000	.944	.998

Table 5: Association between Gleason and PSA categories

Gleason Grade		PSA Categories		Total
		2	3	
1	N	5	14	19
	%	26.3%	73.7%	100.0%
2	N	3	2	5
	%	60.0%	40.0%	100.0%
3	N	1	5	6
	%	16.7%	83.3%	100.0%
4	N	1	2	3
	%	33.3%	66.7%	100.0%
5	N	1	1	2
	%	50.0%	50.0%	100.0%
Chi Square		3.06		
p value		0.55		

Table 6: Association between Gleason and pirads categories

Gleason grade		PIRADS (V2) CATEGORY				Total
		2	3	4	5	
1	N	4	6	7	2	19
	%	21.1%	31.6%	36.8%	10.5%	100.0%
2	N	0	3	1	1	5
	%	0.0%	60.0%	20.0%	20.0%	100.0%
3	N	0	3	2	1	6
	%	0.0%	50.0%	33.3%	16.7%	100.0%
4	N	0	0	0	3	3
	%	0.0%	0.0%	0.0%	100.0%	100.0%
5	N	0	0	0	2	2
	%	0.0%	0.0%	0.0%	100.0%	100.0%
Chi Square		21.27				
p value		0.05				

DISCUSSION

Over the past decade, significant advances have been made in the clinical utility of multiparametric MRI (MpMRI) for identifying suspicious areas indicative of prostate cancer.[8,17] Yet, the role of MpMRI specifically in men with PSA levels between 4-10 ng/ml remains less explored. Prior to the establishment of a standardized reporting system for prostate MRI, Tamada et al.[11] assessed the individual and combined efficacy of T2-weighted, dynamic contrast-enhanced, and diffusion-weighted sequences in a cohort of 50 cases with gray zone PSA. They reported a per-patient sensitivity and specificity of 83% and 80%, respectively.

Further studies by Perdona et al.[18] on patients with PSA < 10 ng/ml, utilizing MR spectroscopy combined with dynamic contrast-enhanced sequences, concluded a sensitivity of 71% and a specificity of 48%, along with a negative predictive value of 91% and a positive predictive value of only 19%. The advent of the PI-RADS system and its subsequent update to PI-RADS version 2.[9] have revolutionized prostate MRI reporting, incorporating T2-weighted and two functional MRI sequences

(Diffusion-Weighted and Dynamic Contrast Enhanced), while omitting MR spectroscopy.

Our current study leveraged PI-RADS version 2, demonstrating an MpMRI sensitivity and specificity of 100% and 84.59%, respectively, for overall cancer detection. For clinically significant prostate cancers, sensitivity remained at 100%, with negative and positive predictive values of 85.89% and 78.57%, respectively. This enhanced diagnostic performance, in comparison to the studies by Tamada,[11] and Perdona,[18] is likely due to the standardized reporting and reduced interobserver variability afforded by PI-RADS version 2.

Moreover, the negative predictive value (NPV) of MpMRI in our study was impressive, with 85.89% for overall cancer detection and 72.37% for clinically significant prostate cancer, aligning with previous literature supporting the high NPV of MpMRI.[21,22] Lu AJ et al,[20] noted an NPV of 73% in their cohort of 100 men with a negative MpMRI, reinforcing the reliability of MpMRI in excluding prostate cancer.

Our findings also underscored the high diagnostic accuracy of MpMRI in higher PI-RADS categories. All cases within PI-RADS categories 4 and 5 were correctly identified as malignant, and 80% of category 3 cases were diagnosed as prostate cancer, with only 20% identified as benign prostatic hyperplasia due to the technical limitations of PI-RADS scoring.

Interestingly, our study confirmed the benign nature of PI-RADS category 1 in all cases (100%), which could potentially guide clinical decisions to forego biopsy in such low-risk cases, thus avoiding the associated costs, complications, and patient anxiety. However, the detection of malignancy in 15.38% of PI-RADS category 2 cases highlights a limitation of MpMRI, emphasizing the need for cautious interpretation in lower PI-RADS categories.

To our knowledge, this is the first study to integrate MpMRI with PSA testing in the specific cohort of men with PSA levels of 4-10 ng/ml. This group presents a diagnostic challenge, and our findings could significantly inform clinical decision-making, potentially reducing unnecessary biopsies and improving patient management in this gray zone of PSA levels.

CONCLUSION

In our cohort of men with PSA between 4-10ng/ml we found that MpMRI had very high sensitivity and specificity and accuracy for detection of prostate cancer. None of the clinically significant cancers were missed by MpMRI. In our experience use of MpMRI could have avoided 67.59 % of unnecessary biopsies without missing any of cancers. Although it needs further validation studies with greater sample size but the information from this study should help guide recommendations to patients in gray zone PSA range about undergoing systematic TRUS-guided biopsy.

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