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The Diagnostic Performance of Multiparametric Magnetic Resonance Imaging to Detect Significant Prostate Cancer

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Abstract

Introduction: To assess the accuracy of multiparametric magnetic resonance imaging (mpMRI) for significant PC detection before diagnostic biopsy in men with abnormal PSA/DRE.

Material and Methods: 388 men underwent mpMRI including T2-weighted, diffusion-weighted & dynamic contrast-enhanced imaging prior to biopsy. Two radiologists used PIRADS reporting system to allocate a score of 1–5 for suspicion of significant PC (Gleason 7 with >5% grade 4). PIRADS score 3-5 was considered positive. Transperineal template-guided mapping biopsy of 18-regions (median 30 cores) were performed, with additional manually directed cores from MRI-positive regions. The anatomical location, size, and grade of individual cancer areas in the 18-biopsy regions, as primary outcome, and in prostatectomy specimens (n=117), as secondary outcome, were correlated to the MRI-positive regions.

Results: Of the 388 men that were enrolled, 344 were analyzed. mpMRI was positive in 77.0% of patients, 62.5% had PC and 41.6% had significant PC. Detection of significant PC by mpMRI had sensitivity of 96%, specificity of 36%, NPV and PPV were 92% and 52%. Adding PIRADS to the multivariate model including PSA, DRE, prostate volume and age improved the AUC from 0.776 to 0.879, $p<0.001$. Anatomical concordance analysis showed a low mismatch between the MRI-positive regions and biopsy-positive regions (n=4(2.9%)), and the significant PC area in RP specimen (n=3(3.3%)).

Conclusions: In men with abnormal PSA/DRE, mpMRI detected significant PC with an excellent NPV and moderate PPV. The use of mpMRI for diagnosing significant PC may result in a substantial number of unnecessary biopsies while missing minimum number of significant PC.

Introduction

Early detection and management of prostate cancer (PC) is one of the most challenging and controversial issues in medicine. Currently, the standard of care for men with elevated prostate-specific antigen (PSA) levels or abnormal digital rectal examination (DRE) is a 12-core template systematic transrectal ultrasound (TRUS) guided biopsy[1, 2]. The limitations of this biopsy strategy are a relatively low yield of tumours[3], failure to detect significant PC[4], inaccurate tumour risk stratification[5], and the over-detection of insignificant PC[6].

Multiparametric magnetic resonance imaging (mpMRI) provides the best anatomic and functional imaging of the prostate compared to other imaging methods[7]. The positive predictive value of significant PC detection with mpMRI is 20-68%, which is considerably higher than random systematic TRUS guided biopsy[8-11]. The reported sensitivity of mpMRI for significant PC is 76-96%[8-11]. However, most studies are limited by their retrospective design, lack of standardized mpMRI scanning and reporting protocols, the use of targeted biopsies, 12-core TRUS-guided biopsies or radical prostatectomy alone as the reference standard, each of which has limitations due to detection, ascertainment and selection biases. In addition, most studies failed to report lesion specific correlation between the region of interests (ROI) on mpMRI and histopathology[8].

To overcome these limitations, the ideal study design to determine the diagnostic accuracy would constitute standardized double-reported mpMRI followed by grid-directed transperineal template mapping biopsy (TTMB) and validated against whole-mount sectioned radical prostatectomy (RP) specimens as the reference standard in those undergoing RP. Since performing RP in all study participants-including those with no cancer or insignificant cancer on biopsy would be

unethical, TTMB is considered the best available reference standard[12, 13]. The aim of this prospective cross-sectional study was to determine the overall and lesion-specific accuracy of mpMRI for significant PC detection before diagnostic biopsy in men with abnormal PSA or DRE, using TTMB as the reference.

Materials and methods

Characterization of the study population

Between April 2012 and March 2014, a total of 388 men were enrolled in this prospective cohort. Selection criteria included men aged over 40 years, planned for biopsy for abnormal PSA or DRE, life expectancy greater than 10 years, and no previous prostate MRI or biopsy. Institutional review board approval was granted (SVH12/007) and informed consent was obtained in all patients before MRI and biopsy. Data was reported according to the START criteria[14]. Figure 1 presents a flow diagram of the patient selection.

Study protocol

The study and MRI protocol is described in detail in Thompson et al[15]. In summary, all mpMRIs were performed at 2 centers (1.5 Tesla magnet (b-value 0-$800 s/\mathrm{mm}^2$) at centre 1 and 3 Tesla magnet (b-value 0-1500s/mm^2) at centre 2) using a standard MRI protocol described in[16]. According to the study protocol, two radiologists double reported independently, and were blinded to each other. General agreement (each scoring PIRADS 1 or 2, or 3 to 5) between the two radiologists was 75%, quadratic weighted κ was 0.63[15]. The standardized 5-point Prostate Imaging Reporting and Data System (PIRADS) scale was used[16]. Using objective criteria ROIs were assigned a score of 1 to 5 for each parameter (T2WI, DCEI and DWI) and then an overall impression ROI score (based on individual parameter scores). MRI-derived ROIs were indicated on a topographic map with 18 MRI-regions corresponding to biopsy template locations (Figure 2a).

All participants underwent TTMB (median of 30 cores with relative peri-urethral zone sparing and adjusted for volume) from 18 template locations (Figure 2a). Urologists reviewed the MRI report and images, and collected two additional targeted cores from all ROIs potentially under sampled by template biopsy using 2 methods:

1) MRI/TRUS fusion biopsy was performed with a floor mounted, transperineal grid TRUS platform (BK Medical, Herlev, Denmark) combined with Biojet rigid MRI/TRUS fusion software (Meditron, Melbourne, Victoria, Australia) for ROIs potentially missed by cognitive targeted biopsy due to a diameter of less than 10 mm and a site outside the template.

2) Cognitive (manual MRI informed) transperineal grid directed, TRUS guided biopsy was done for ROIs with a diameter of 10 to 15 mm at an easily accessible location but that were potentially under sampled by template biopsy. Such ROIs were generally visible on TRUS as a hypoechoic area, aiding cognitive targeted biopsy. Targeted biopsy was unnecessary for large ROIs greater than 15 mm in diameter that spanned multiple template locations since they were covered by at least 2-3 template cores.

Histology from biopsies and RPs were processed and reported according to ISUP (International Society of Urological Pathology) protocols by one uropathologist. RP specimens were processed following the protocol described previously[17]. Tumor areas were marked at each slide and measured using 3D volume estimation. Each tumour focus detected was outlined on a topographic map with regions corresponding to the MRI-positive regions (Figure 2b).

Correlation of mpMRI images with histopathologic findings in TTMB and RP specimens was assessed[18, 19]. In our study, we applied the following analytic approach to correlate each mpMRI with TTMB and RP specimen. Firstly, the MRI-positive ROIs were assessed and correlated with the location of the positive TTMBs in order to assess anatomical concordance or mismatch (definitions

Figure 4), with cores in the same zone and in zones with direct contact as considered part of the same lesion (Figure 2a). For example, each sector had either three or five neighbors, depending on the location, with the tumour focus considered to correlate even if it was present in a direct neighboring sector. Secondly, any additional positive TTMB was assessed and indicated as an additional separate significant PC in another region, which was missed on mpMRI, if the PC was found in a region not directly adjacent to the MRI-positive ROIs and index tumour. In RP specimens, firstly, the MRI-positive regions were assessed and correlated with the location of the index tumour to assess anatomical concordance or mismatch. For this correlation, we also took the direct neighboring regions into account, meaning that the tumour focus was considered to correlate even if it was present in the direct adjacent 18-core region (Figure 2b). Secondly, any additional tumour focus detected in the RP specimen was assessed and indicated as an additional separate significant PC in another region, which was missed on mpMRI, if the significant PC had an estimated 3D tumour volume of >0.2ml and was found in a region not directly adjacent to the index tumour.

Statistical analysis

Significant PC on biopsy was defined as any PC of Gleason score 7-10 with greater than 5% Gleason grade 4, ≥ 15% cores positive or ≥ 7mm of PC in any core. Alternative definitions 1-4 were selected prospectively to facilitate future comparison with other studies (Appendix 1). Binary overall PIRADS (1 or 2—negative and 3 to 5—positive), biopsy (primary end point) and prostatectomy (secondary end point) significant cancer variables were defined for chi-square analysis. The Cochran-Armitage trend test was used to assess the association between PIRADS score and significant cancer at biopsy. Analysis was stratified by prebiopsy risk with lower risk defined as PSA <10 ng/ml and normal DRE, and higher risk defined as PSA ≥10 ng/ml and/or abnormal DRE. Stepwise logistic regression and AUC analysis were done to explore the relationship between overall PIRADS score (1 to 5) and significant cancer adjusting for age, PSA,

DRE, family history, prostate volume estimated on mpMRI, magnet strength (1.5/3.0 Tesla) and radiologist (1/2). All statistical tests were two-sided. A p value <0.05 was considered statistically significant. Analyses were performed using SPSS version 22.

Results

Complete data were available for 344 patients (Figure 1). Patients' characteristics are presented in Table 1.

Cancer detection rates from biopsy

In total 265 (77.0%) men had a positive mpMRI, 215 (62.5%) men were diagnosed with PC, 143 (41.6%) with significant PC. Table 2 shows the relationship between PIRADS score and the likelihood of a positive biopsy. The sensitivity and specificity of a positive mpMRI for the detection of significant PC at biopsy was 96% and 36% respectively (Table 3). The negative predictive value (NPV) and positive predictive value of a positive mpMRI for the detection of significant PC was 92% and 52% respectively. Diagnostic performance was not significantly different between the 1.5 and 3.0 Tesla magnet, OR 0.84 (95%CI 0.48-1.47,p=0.53).

Clinical risk stratification

PSA, DRE, age, prostate volume and PIRADS score were strongly associated with significant PC on univariate analysis (each p<0.005), whereas family history was not (p=0.85). On multivariate analysis PIRADS (p<0.001), PSA (p=0.001), DRE (p=0.029), age (p<0.001) and prostate volume (p=0.002) were independent predictors. Magnet strength (p=0.9) and family history (p=0.1) were not and, therefore, they were removed from the final model. Adding PIRADS (1-5) to the base model of PSA, DRE, prostate volume and age increased the AUC significantly for predicting significant PC from 0.776 to 0.879 (95%CI 0.843–0.916, Figure 3).

Performance of mpMRI in high-risk men and patients with normal DRE

The NPV and PPV of mpMRI for significant PC detection among 159 men with a pre-biopsy PSA ≥ 10.0 ng/ml or an abnormal DRE was 100% and 64%, respectively. In this subgroup, mpMRI demonstrated low specificity of 26% and would have saved only 11% of men from an unnecessary biopsy, however it did not miss any significant PC. Among all men (n=185) with a normal DRE and PSA <10.0 ng/ml, the NPV and PPV was 90% and 37% for detection of significant PC. In this subgroup, mpMRI would save 27% of men from an unnecessary biopsy while missing or delaying the diagnosis of significant PC in only 3% of men.

Cancers missed on mpMRI

Only 6 significant PC were missed on mpMRI. Patient characteristics are listed in Table 4. All missed significant PC were intermediate risk, with Gleason scores of 3+3 or 3+4 and had no abnormal findings on DRE.

RP specimen analysis

RP was performed on 117 men, median age 64 years, PSA 5.6 ng/ml. The mpMRI was positive in 109 (93%) of these men. In total 95 (87%) of the 109 men harbored a significant PC based on their RP specimen. Agreement between significant PC classification in biopsies and RP was 81.2%; 12% was upgraded from low risk PC at biopsy to significant PC according to their RP specimen, 6.8% was downgraded from significant PC in biopsies to insignificant PC based on the RP specimen.

Anatomical concordance analysis

An 18-region anatomical concordance analysis was determined among 265 men with positive ROIs on mpMRI and the location of the positive TTMB, and among 109 men who underwent a RP between the positive ROIs on mpMRI and area of significant PC in RP specimen. Results are presented in Figure 4. Overall, anatomical concordance of mpMRI with 18-region biopsy template was found in

97% of men diagnosed with significant PC, with only in 3% of these men a true positive biopsy but anatomical mismatch with the MRI-positive region (1 in the anterior apex, 1 in the posterior apex, and 2 in the base/mid posterolateral). In 11% of men with significant PC, we found true positive concordance between the MRI-ROI and biopsy, but there was an additional separate region of significant PC found in another region on biopsy but not reported on MRI. In no case did the separate significant lesion have a higher tumour grade or volume than the index tumour that correlated with the MRI. In the 109 men who underwent MRI and had a ROI on mpMRI, anatomical concordance analysis demonstrated true positive concordance in 97% of the cases, with only in 3% of the men an anatomical mismatch. In 13% of men there was true positive concordance but was a separate additional significant PC found elsewhere in the RP specimen that was not reported on MRI. In no case did the separate significant PC have a higher tumor grade or volume than the index tumour.

Discussion

In this study, mpMRI detected significant PC with a high sensitivity and limited specificity. If these results are validated by other studies, routine pre-biopsy mpMRI could improve the detection of clinically significant PC while avoiding unnecessary biopsies in 23% of patients, and enhance the detection of clinically low-risk PC by 34% (215(100%) PC detected - 143(66%) significant PC detected = 34% non-significant PC detected). Importantly, using the second most optimal reference test, TTMB, this prospective trial showed that mpMRI only missed or delayed the diagnosis of significant PC in a small percentage of patients.

This study adds key information to the value of mpMRI for the diagnosis of significant PC and to the dilemma if targeted prostate biopsies have similar diagnostic accuracy as systematic random prostate biopsies, and can replace them. It showed that the index lesion can be identified in most men. The determined anatomical mismatch between the ROI and detection of significant

PC was low (4/265 men), supporting studies that have shown the superiority of targeted biopsy over systematic random template biopsies to decrease the detection of low-risk while increasing the detection of significant PC[20-22]. In 11% to 13% of patients an additional significant PC was found elsewhere in the prostate that was not reported on mpMRI, and supports the feasibility of selective targeted therapy that involves only the index lesion rather than the whole prostate[23].

Numerous studies have shown the high NPV of mpMRI for detecting significant PC using 12-cores, saturation or RP specimen as reference tests[7, 11, 24, 25]. The PPV varies between 20-68% and is strongly related to the reference test used, the patient population examined, and the definition of a positive MRI. We defined PIRADS 3 also positive, although PIRADS 3 is defined as intermediate, meaning the presence of clinically significant cancer is equivocal. However, since we aimed to evaluate mpMRI as an early detection tool for significant PC, we precedence the sensitivity (minimize missing significant PC) over specificity. Nevertheless, our results underline that improvement in the performance of mpMRI is needed. In the current study, the overall PPV of mpMRI for detecting significant PC was 36% with saving 23% of the men from an unnecessary biopsy. Obviously, improvement is needed in the lesions classified as PIRADS 3. Possibly, pseudo-quantitative T2WI MRI will provide a quantitative assessment in this patient group[26]. Furthermore, improving the T2WI technique and additional interpretation training will probably further increase the specificity of mpMRI for the diagnosis of significant PC.

Some limitations need to be discussed. Firstly, we used grid-directed TTMBs as the reference test, with still the risk of missing or misclassifying some cancers as indicated in the validation study by Huo et al[27]. Secondly, no follow-up is available in men with a negative TTMB. Third, for anatomical correlation the tumor focus was considered to correlate even if it was present in a direct adjacent region. A more stringent approach is used by other groups, however, in

our opinion, the present approach allows the determination of accuracy within a certain distance range without observer bias from the urologist, radiologist or pathologist. Finally, since all mpMRIs were reported by very experienced radiologists, both reported more than 1000 prostate mpMRIs before, the present results may not be directly adaptable to clinical practice. Obviously, validation of our results in a general clinic with less experienced radiologist is indicated.

Conclusions

In men with abnormal PSA/DRE, mpMRI detected significant PCa with an excellent NPV and moderate PPV. Additional validation studies are needed to determine if mpMRI targeted biopsy have the potential to replace the systematic random prostate biopsies, and to decrease unnecessary biopsies and overdetection of low risk PC while maintaining a low rate of missed significant PC.

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Table 1. Baseline characteristics of analyzed study population 344 men

Characteristics	Median (IQR)	% Patients
Age, years	62.9 (55.9-67.1)	-
PSA, ng/ml	5.2 (3.7-7.1)	-
Abnormal DRE	-	44.4
First-degree relative with PC	-	26.7
Magnet strenght (Tesla): 1.5 3.0	 - -	 49.4 50.6
Median volume MRI, cm^3	40.0 (30.0-54.0)	
Pos MRI PIRADS 3-5	-	77.0

Table 2: PIRADS mpMRI score and biopsy risk category

		% Patients			
PIRADS mpMRI score	**Total patients, n**	**No PC**	**Low Risk**	**Intermediate risk**	**High Risk**
1	14	2.6	1.4	0	0
2	65	12.8	4.3	1.7	0
3	139	18.3	10.7	8.4	2.9
4	89	3.8	4.3	11.9	5.8
5	37	0	0	5.8	4.9
Total	344	37.5	20.9	27.9	13.7

Low grade PC biopsy: PC Gleason score 6-7 with 5% or less Gleason grade 4 + less than 30% cores positive + less than 8mm max core length PC. Intermediate PC biopsy: Gleason score 7 with greater than 5% Gleason grade 4 + less than 50% of cores positive or Gleason 6-7 with 5% or less Gleason 4+ either 30% or greater of cores positive or 8 or greater mm max core length of PC. High grade PC biopsy: Gleason score 7 + greater than 5% Gleason grade 4 + greater than 50% of cores positive or Gleason 8-10.

Table 3: Sensitivity, Specificity, NPV and PPV of mpMRI PIRADS 3-5 detection of PC

	PC biopsy			Significant PC biopsy			Significant PC biopsy strict criteria		
PIRADS	**3-5**	**4-5**	**5**	**3-5**	**4-5**	**5**	**3-5**	**4-5**	**5**
Sensitivity	88	53	17	96	68	26	94	63	23
Specificity	41	90	100	36	86	100	38	85	100
NPV	67	53	42	92	79	65	89	73	61
PPV	71	90	100	52	78	100	56	79	100
Significant PC biopsy: Any PC of Gleason score 7-10 with greater than 5% Gleason grade 4, ≥ 15% cores positive or ≥ 7mm of PC in any core. Significant PC biopsy strict criteria: Any PC of Gleason score 7-10, ≥ 10% cores positive or ≥ 5mm of PC in any core									

Table 4. Features of significant PC missed on mpMRI

Patient ID	PIRADS	Risk Category	Gleason Score	Max core length (mm)	% cores positive	PSA ng/ml	DRE
9	2	Intermediate	6	8	29	3.7	T1c
155	2	Intermediate	7 (10% 4)	6	11	5.4	T1c
44	2	Intermediate	7 (10% 4)	7	12	6.3	T1c
300	2	Intermediate	7 (10% 4)	12	33	5.1	T1c
294	2	Intermediate	7 (30% 4)	1	7	4.9	T1c
298	2	Intermediate	7 (40% 4)	1	9	3.4	T1c

Figure 1. Flow chart selection patients study population

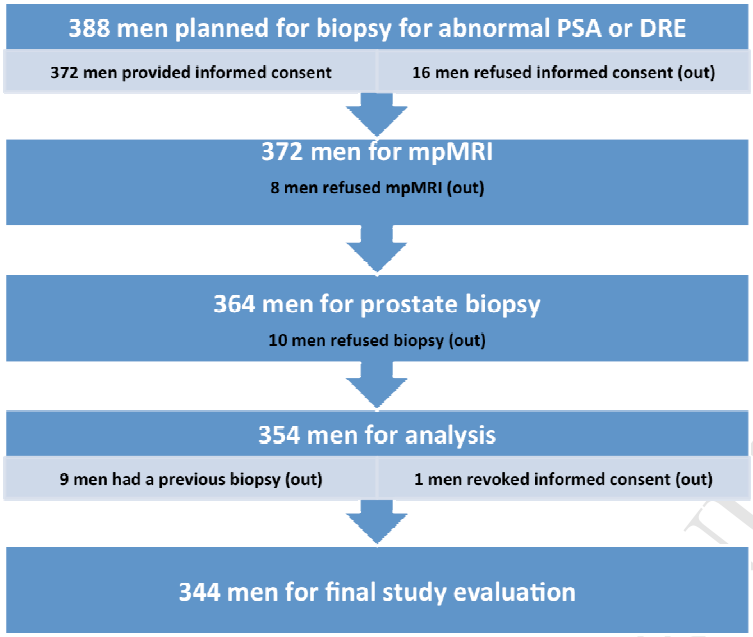
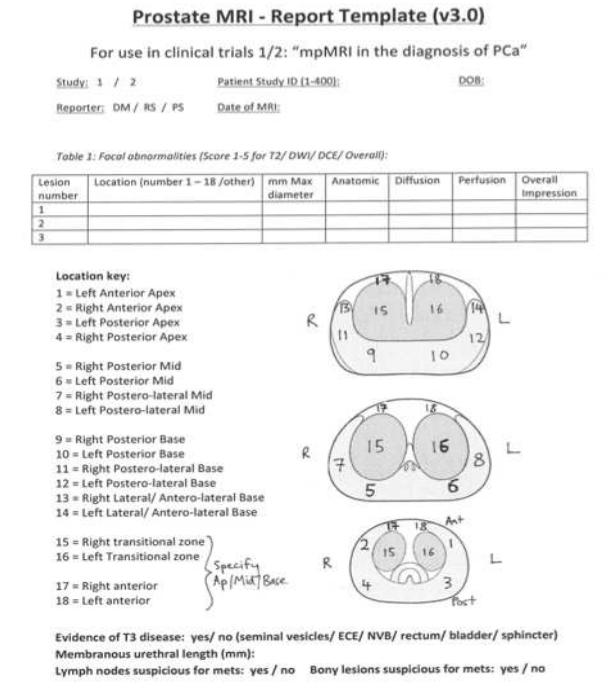


Figure 2a. Standardized PIRADS based reporting template for study mpMRIs. Bx, biopsy. Ap, apex. ECE, extracapsular extension. NVB, neurovascular bundle. mets, metastasis.



Prostate MRI - Report Template (v3.0)

For use in clinical trials 1/2: "mpMRI in the diagnosis of PCa"

Study: 1 / 2 Patient Study ID (1-400): DOB:

Reporter: DM / RS / PS Date of MRI:

Table 1: Focal abnormalities (Score 1-5 for T2/ DWI/ DCE/ Overall):

Lesion number	Location (number 1 – 18 /other)	mm Max diameter	Anatomic	Diffusion	Perfusion	Overall Impression
1						
2						
3						

Location key:
1 = Left Anterior Apex
2 = Right Anterior Apex
3 = Left Posterior Apex
4 = Right Posterior Apex

5 = Right Posterior Mid
6 = Left Posterior Mid
7 = Right Postero-lateral Mid
8 = Left Postero-lateral Mid

9 = Right Posterior Base
10 = Left Posterior Base
11 = Right Postero-lateral Base
12 = Left Postero-lateral Base
13 = Right Lateral/ Antero-lateral Base
14 = Left Lateral/ Antero-lateral Base

15 = Right transitional zone
16 = Left Transitional zone

17 = Right anterior
18 = Left anterior

Specify Ap/Mid/Base

Evidence of T3 disease: yes/ no (seminal vesicles/ ECE/ NVB/ rectum/ bladder/ sphincter)
Membranous urethral length (mm):
Lymph nodes suspicious for mets: yes / no Bony lesions suspicious for mets: yes / no

Figure 2b. Standardized prostatectomy graphical synaptic report.

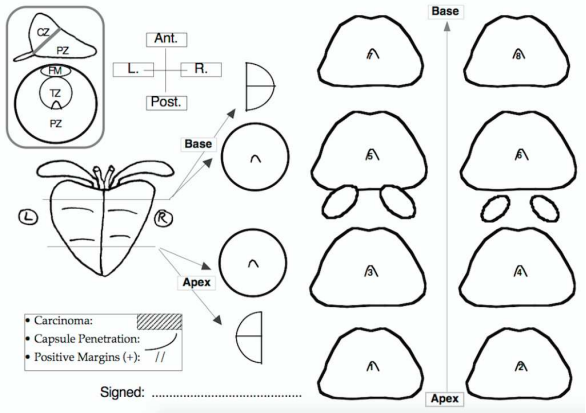


Figure 3. AUCs of multivariate base model (PSA+DRE+prostate volume+age) with and without mpMRI PIRADS to predict significant PC at biopsy.

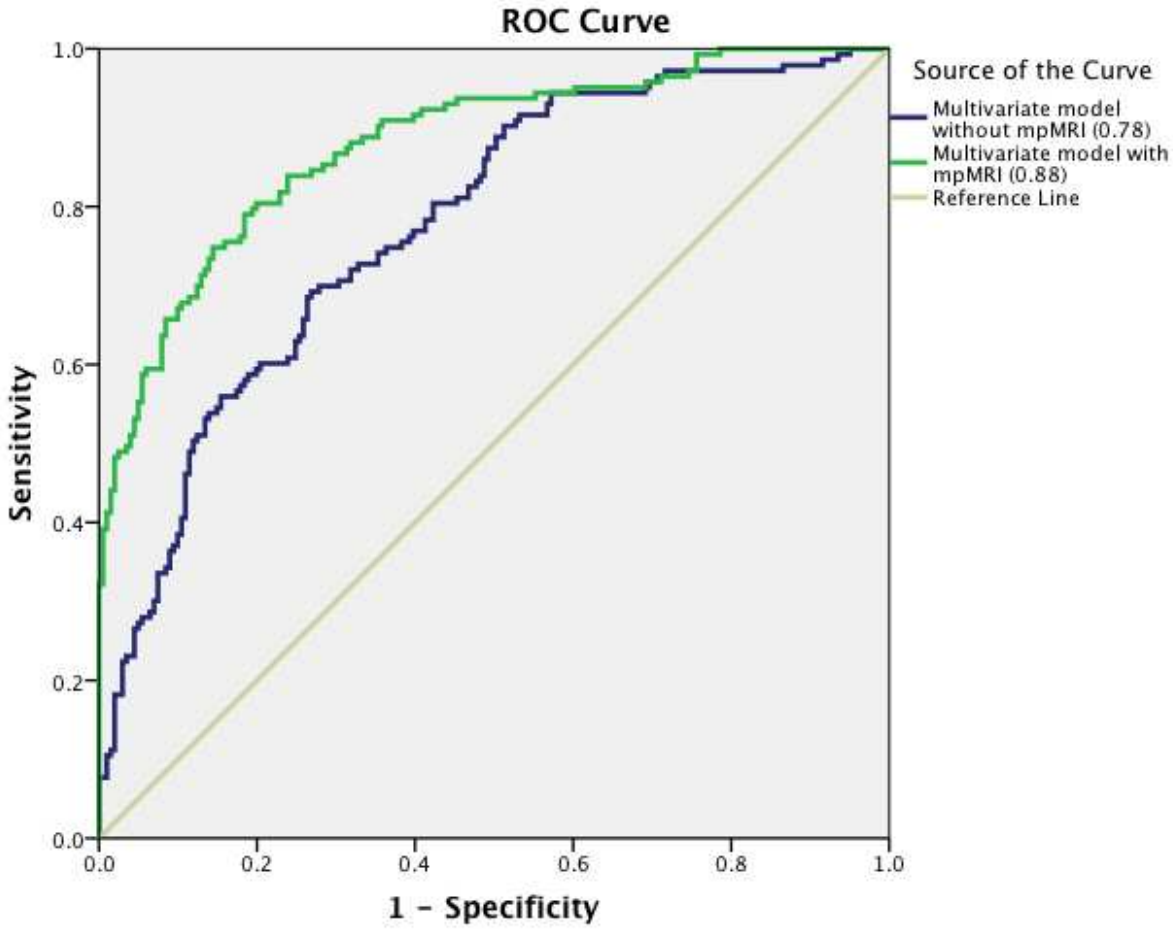
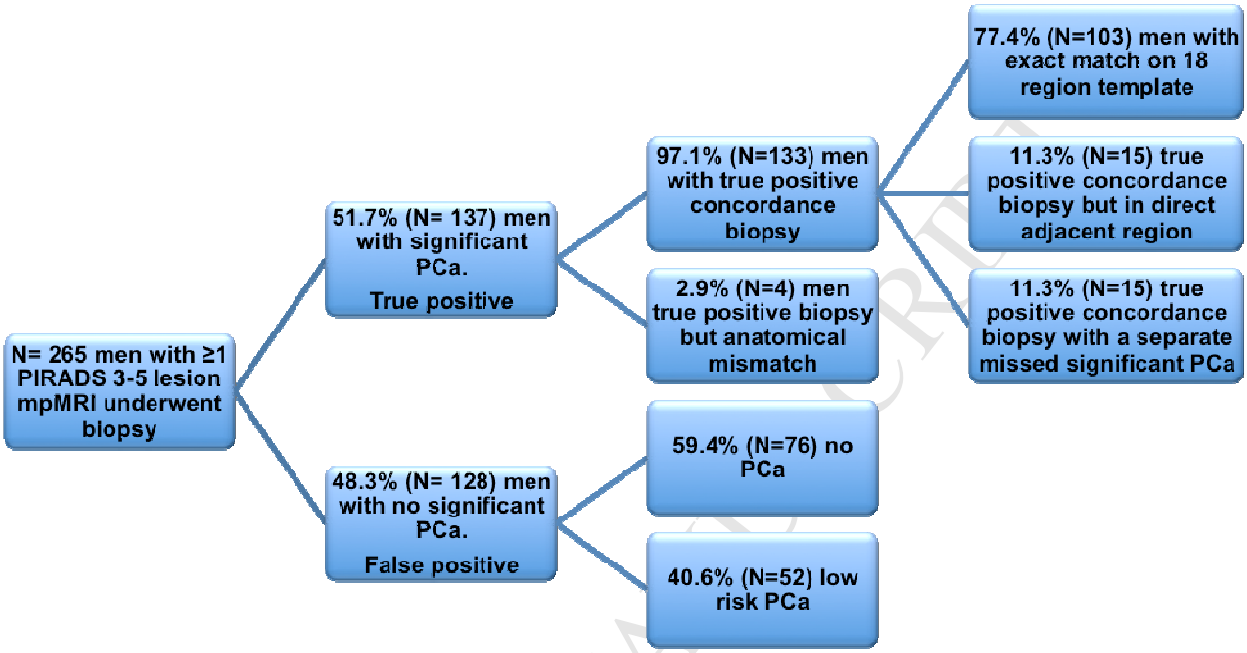
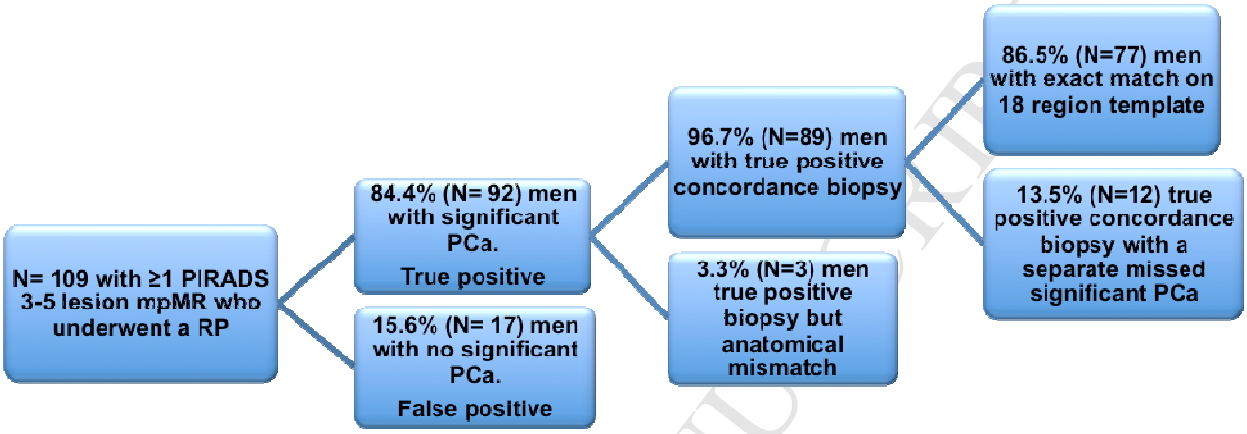


Figure 4a. Anatomical concordance MRI-suspicious regions and 18 biopsy regions.



Definitions used in Figure 4a: True positive concordance biopsy = Positive ROI on MRI index location matches index biopsy location with anatomical concordance. True positive concordance biopsy but in direct adjacent region = Positive ROI on MRI index location matches with the direct adjacent index biopsy location of the 18 regions biopsy template locations. True positive biopsy but anatomical mismatch = MRI positive but doesn't match with the biopsy index location of the 18 regions biopsy template. True positive concordance biopsy with a separate missed significant PC = Positive ROIs on MRI index location matches index biopsy location with anatomical concordance but additional separate significant PC in another region on biopsy which was missed on mpMRI.

Figure 4b. Anatomical concordance MRI-suspicious regions and cancer areas in radical prostatectomy specimens.



Definitions used in Figure 4b: True positive concordance RP = Positive ROI on MRI index location matches index RP location with anatomical concordance. True positive biopsy but anatomical mismatch = MRI positive ROIs but doesn't match with the biopsy index location of the 18 regions biopsy template. True positive concordance biopsy with a separate missed significant PC = Positive ROIs on MRI index location matches index RP location with anatomical concordance but additional separate significant PC in another region in RP specimen which was missed on mpMRI. Additional separate significant PC defined as any Gleason score 8-10, Gleason score 7 and tumorvolume >0.2cc, Gleason score 6 and tumorvolume >0.5cc.

Appendix 1. Four definitions of biopsy based risk categories

	PC Risk Category		
Definition	Low	Moderate	High
1. More strict, grade only criteria	Gleason score 6	Gleason score 7	Gleason score 8-10
2. Less strict, grade only criteria	Gleason score 6-7 with 5% or less Gleason grade 4	Gleason score 7 with greater than 5% Gleason grade 4	Gleason score 8-10
3. More strict grade + vol criteria	Gleason score 6 + less than 20% of cores pos + less than 5 mm max core length PC	Gleason score 7 + less than 50% of cores pos or Gleason score 6 + either 20% or greater of cores pos or 5 mm or greater max core length of PC	Gleason score 7 and greater than 50% of cores pos or Gleason score 8-10
4. Less strict grade + vol criteria	Gleason score 6-7 with 5% or less Gleason grade 4 + less than 30% of cores pos + less than 8 mm max core length PC	Gleason score 7 with greater than 5% Gleason grade 4 + less than 50% of cores pos or Gleason score 6-7 with 5% or less Gleason grade 4 + either 30% or greater of cores pos or 8 or greater mm max core length of PC	Gleason score 7 + greater than 5% Gleason grade 4 + greater than 50% of cores pos or Gleason score 8-10
The accuracy of mpMRI for the detection of significant PC was determined using these different definitions. The sensitivity for the detection of significant PC ranged from 92 to 96%, specificity 34-38%, NPV 92-96% and PPV 46-56%.			

List of abbreviations

DRE = digital rectal examination
mpMRI= multiparametric magnetic resonance imaging.
NPV = negative predictive value
PC = prostate cancer
PIRADS = prostate imaging reporting and data system.
PPV = positive predictive value
PSA = prostate specific antigen
ROI = region of interest
RP = radical prostatectomy
TRUS = transrectal ultrasound
TTMB = transperineal template mapping biopsy