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Research Communication

Risk-adapted biopsy decision based on prostate magnetic resonance imaging and prostate-specific antigen density for enhanced biopsy avoidance in first prostate cancer diagnostic evaluation

Prostate MRI has been integrated into the diagnostic evaluation for men at risk of having clinically significant cancer in multiple clinical care guidelines. Owing to the low false-negative rate of prostate MRI accompanying a sensitivity averaging 91%, we can reduce biopsies (by 30%) and indolent cancer detection, while maintaining (or even improving) detection of significant cancers compared to systematic biopsy [1]. Reducing false-negative MRI results further remains a clinical priority, calling for risk-adapted strategies for patient biopsy selection [2,3]. Multivariable risk-prediction tools incorporating MRI results have been developed [4], but remain unvalidated.

Multiple publications advise the combination of MRI findings and PSA density (PSAD) for defining men who can safely avoid biopsy [5,6]. In the present analysis, we extract in biopsy-naïve men, the data relating to prostate MRI results and PSAD values to the likelihood of clinically significant disease. We propose a simple, risk-adapted advice for biopsy avoidance, based on current urological guideline thresholds. Our analyses are meant to be hypothesis generating, requiring prospective validation.

Using PubMed/Ovid-MEDLINE literature searches (up to May 2020), studies on biopsy-naïve men undergoing systematic and where indicated MRI-directed targeted biopsies at the same time, that provided three or four PSAD risk categories in the low-, intermediate- and high-risk range were found and related to Prostate Imaging-Reporting and Data System (PI-RADS) scores [5–9]. Studies using a single threshold for PSAD or binary MRI classification (positive/negative) were excluded, as were multivariate studies using PSADs. We also excluded studies that only included selected negative or equivocal MRI studies without prevalence data.

In total, 3006 biopsy-naïve men in five studies were included (study characteristics Table S1). The overall prevalence of significant disease (International Society of Urological Pathology [ISUP] ≥2 cancers) among studies was 39% (range 28–49%).

The population was stratified into four (or three; rates between brackets) PSAD risk groups (Table 1 [5–10): <0.10, 0.10–0.15, 0.15–0.20, and >0.20 ng/mL/mL, corresponding to 31% (29%), 28%, 16%, and 25% (27%) of the whole population; with ISUP ≥2 cancer detection rates of 11% (14%), 28%, 47%, and 66% (68%), respectively.

The population was also stratified into three PI-RADS category risk groups: PI-RADS 1–2 (low risk), 3 (intermediate risk), and 4–5 (high risk), corresponding to 38% (36%), 12% (14%), and 50% (51%) of whole study population, with ISUP ≥2 detection rates of 6% (9%), 16% (22%), and 62% (65%), respectively (Table 1).

MRI-negative men (PI-RADS 1–2) with a low-risk PSAD (<0.10 ng/mL/mL) have a 3% (4%) risk of significant disease (Table 1, Fig. S1a). MRI-negative men with intermediate–low (0.10–0.15 ng/mL/mL) or intermediate–high risk PSAD (0.15–0.20 ng/mL/mL) have respectively 7% and 8% risk of significant disease. MRI-negative men with a high-risk PSAD (>0.20 ng/mL/mL) have 18% (24%) risk of significant disease. These data suggest that MRI-negative men with low-risk PSADs can avoid biopsies all together (lower than average population risk [<5%] [10]). Additionally, using the European Association of Urology (EAU)/National Institute for Health and Care Excellence (NICE)/AUA recommendations, MRI-negative men with a PSAD of 0.10–0.15 or 0.15–0.20 ng/mL/mL may avoid immediate biopsy with an adequate safety-net of monitoring as part of shared decision-making. However, MRI-negative men with a high-risk PSAD (>0.20 ng/mL/mL) require systemic biopsies, despite the absence of visible MRI-targets (Fig. S1a).

Men with indeterminate PI-RADS 3 scores and a low-risk PSAD (<0.10 ng/mL/mL) have a low 4% (9%) risk of significant disease, and biopsies could be avoided (Table 1, Fig. S1a). Men with PI-RADS 3 scores and a high-risk PSAD (>0.20 ng/mL/mL) have an elevated 29% (36%) risk, and targeted and systematic biopsies should be taken.

MRI-positive men with PI-RADS 4–5 category scores, irrespective of PSAD-risk categories, should undergo targeted with or without systematic biopsies (EAU recommendations). Indeed, PI-RADS 4–5 category scores were found in 189 of 674 (28%) men with low-risk PSAD values (<0.10 ng/mL/mL); in these men, 31% were found to have significant disease, indicating that biopsies should be taken in men with low PSAD values when MRI scans are positive.

Table 1 Risk data table of clinically significant prostate cancer (csPCa), related to PI-RADS score and PSAD categories in biopsy-naïve men, clinically suspected of having significant disease.

			Detection of clinically significant prostate cancer (ISUP grade 2 and higher)							
			PSA-density risk groups 4 categories				PSA-density risk groups 3 categories			
Study	PI-RADS risk categories	Prevalence ISUP ≥ 2 PCa	low	intermediate-low	intermediate-high	high	PI-RADS risk categories	Prevalence ISUP ≥ 2 PCa	low	intermediate	high
			< 0.10	0.10 - 0.15	0.15 - 0.20	≥ 0.20			< 0.10	0.10 - 0.20	≥ 0.20
					(ng/ml/cm^3)					(ng/ml/cm^3)	
			31% (678/2199)	28% (612/2199)	16% (360/2199)	25% (553/2199)			28% (851/3006)	45% (1357/3006)	27% (798/3006)
Boesen (2019)	PI-RADS 1-2	7% (21/300)	3% (4/139)	7% (7/102)	8% (3/37)	32% (7/22)	PI-RADS 1-2	7% (21/300)	3% (4/139)	7% (10/139)	32% (7/22)
Knaapila (2019)	38%	7% (8/113)	6% (2/32)	8% (3/40)	9% (2/22)	5% (1/19)	36%	7% (8/113)	6% (2/36)	8% (5/62)	5% (1/19)
Van der Leest (2019)	(839/2199)	3% (10/309)	2% (4/165)	3% (3/89)	5% (2/39)	6% (1/16)	(1075/3006)	3% (10/309)	2% (4/165)	4% (5/128)	6% (1/16)
Falagario (2019)		8% (9/117)	2% (1/75)	16% (4/25)	17% (1/6)	27% (3/11)		8% (9/117)	2% (1/75)	16% (5/31)	27% (3/11)
Hansen (2018)								20% (48/236)	9% (6/66)	21% (26/122)	33% (16/48)
Boesen (2019)	PI-RADS 3	19% (23/124)	6% (3/48)	8% (3/40)	53% (9/17)	42% (8/19)	PI-RADS 3	19% (23/124)	6% (3/48)	21% (12/57)	42% (8/19)
Knaapila (2019)	12%	10% (9/90)	0% (0/14)	13% (4/31)	5% (1/19)	15% (4/26)	14%	10% (9/90)	0% (0/14)	10% (5/50)	15% (4/26)
Van der Leest (2019)	(254/2199)	23% (9/40)	0% (0/12)	24% (4/17)	40% (2/5)	50% (3/6)	(407/3006)	23% (9/40)	0% (0/12)	27% (6/22)	50% (3/6)
Hansen (2018)								31% (47/153)	18% (7/38)	31% (28/90)	48% (12/25)
Boesen (2019)	PI-RADS 4-5	62% (239/384)	35% (18/52)	52% (60/115)	65% (53/81)	79% (108/136)	PI-RADS 4-5	62% (239/384)	35% (18/52)	58% (113/196)	79% (108/136)
Knaapila (2019)	50%	72% (212/296)	50% (14/28)	64% (27/42)	72% (48/67)	77% (123/159)	51%	72% (212/296)	50% (14/28)	69% (75/109)	77% (123/159)
Van der Leest (2019)	(1106/2199)	62% (171/277)	36% (20/56)	58% (42/73)	71% (34/48)	75% (75/100)	(1524/3006)	62% (171/277)	36% (20/56)	63% (76/121)	75% (75/100)
Falagario (2019)		*44% (65/149)	*13% (7/53)	*39% (15/38)	*68% (13/19)	*77% (30/39)		*44% (65/149)	*13% (7/53)	*49% (28/57)	*77% (30/39)
Hansen (2018)								71% (297/418)	48% (35/73)	66% (114/173)	86% (148/172)
Compiled totals of csPCa risk											
	PI-RADS 1-2	6% (48/839)	3% (11/411)	7% (17/256)	8% (8/104)	18% (12/68)	PI-RADS 1-2	9% (96/1075)	4% (17/477)	11% (51/482)	24% (28/116)
	PI-RADS 3	16% (41/254)	4% (3/74)	13% (11/88)	29% (12/41)	29% (15/51)	PI-RADS 3	22% (88/407)	9% (10/112)	23% (51/219)	36% (27/76)
	PI-RADS 4-5	62% (687/1106)	31% (59/189)	54% (144/268)	69% (148/215)	77% (336/434)	PI-RADS 4-5	65% (984/1524)	36% (94/262)	62% (406/656)	80% (484/606)
	All PI-RADS	35% (776/2199)	→ 11% (73/674)	28% (172/612)	47% (168/360)	66% (363/553)	All PI-RADS	39% (1168/3006)	14% (121/851)	37% (508/1357)	68% (539/798)
Risk-adapted matrix table for biopsy decision management											
	PI-RADS 1-2		no biopsy	no biopsy	no biopsy	consider biopsy	PI-RADS 1-2		no biopsy	consider no biopsy	highly consider biopsy
	PI-RADS 3		no biopsy	consider biopsy	highly consider biopsy	perform biopsy	PI-RADS 3		no biopsy	highly consider biopsy	perform biopsy
	PI-RADS 4-5		perform biopsy	perform biopsy	perform biopsy	perform biopsy	PI-RADS 4-5		perform biopsy	perform biopsy	perform biopsy

very low	0-5% csPCa (below population risk) #
low	5-10% csPCa (acceptable risk) ##
intermediate-low	10-20% csPCa
intermediate-high	20-30% csPCa
high	30-40% csPCa
very high	>40% csPCa

Thompson IM et al. N Engl J Med. 2004 May 27;350(22):2239-46. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng/ml.

2019 EAU PCa guidelines: csPCa 9% (95%CI: 6-14%)
= accepted risk (MRI sensitivity of 91% (95%CI: 83-95%) and NPV 91% (95%CI:86-94%), at a prevalence of 29% (95%CI:22-38%))

* PI-RADS 3-5 instead of PI-RADS 4-5 category, as this data was not reported, slightly underestimating the actual numbers.

PSA: prostate specific antigen; PI-RADS: prostate imaging reporting and data system; csPCa: clinically significant prostate cancer; ISUP: international Society of Urogenital Pathology grading.

When only considering biopsy at a PSAD of >0.10 ng/mL/mL (without MRI assessments), 31% (28%) of biopsies are avoided at the expense of missing significant disease in 9% (10%) in whole tested population (Table S2). On the other hand, taking the combination of PI-RADS scores with PSAD risk categories described above for biopsy decisions, a total of 38% (36%) biopsies can be avoided at the lower expense of missing significant cancers in 5% (6%) (Table S2).

Overall, a PSAD of >0.20 ng/mL/mL impacts 68 of 839 (8%) MRI-negative men by increasing biopsy procedures (Table 1). A PSAD of <0.10 ng/mL/mL impacts 74 of 254 (29%)

Fig. 1 Risk-adapted matrix table for guidance in biopsy decision, based on PSAD and on MRI risk assessments. The continuum of estimated risks of having a biopsy-detectable prostate cancer are categorised into low- (not elevated), intermediate- and high-risk (elevated). Generally, men at higher risk of having clinically significant prostate cancer require biopsy regardless of how risk is estimated. The MRI risk assessment is categorised into low (PI-RADS 1 or 2), intermediate (PI-RADS 3) or high (PI-RADS 4–5) risk of having a biopsy-detectable clinically significant prostate cancer. Each cell ascribes a different biopsy action, based on the results of Table 1. This matrix table may help guide biopsy-decision management, while awaiting the validation of multivariable MRI prediction tools.

Risk-adapted biopsy decision tool - matrix table			Multivariate risk assessment indicating likely prevalence of clinically significant prostate cancer			
			increasing prevalence →			
		Risk assessment	PSAD (ng/mL/mL)			
			< 0.10	0.10 – 0.15	0.15 – 0.20	≥ 0.20
		MRI score / Risk category	low	intermediate-low	intermediate-high	high
Risk assessment on MRI indicating likely prevalence of clinically significant prostate cancer	↓ increasing prevalence	PI-RADS 1-2 / low	no biopsy	no biopsy	no biopsy	highly consider biopsy
		PI-RADS 3 / intermediate	no biopsy	consider biopsy	highly consider biopsy	perform biopsy
		PI-RADS 4-5 / high	perform biopsy	perform biopsy	perform biopsy	perform biopsy

PI-RADS 3 category men who could avoid biopsies. PSAD does not impact biopsy decisions in PI-RADS 4–5 category men. Therefore, in the combined risk strategy of MRI with PSAD thresholds proposed above, the total number of men avoiding biopsies (38%) is unchanged compared to using only MRI risk assessment (38%), but men are more appropriately selected according to individual risk (Fig. S1a).

This analysis has limitations that require careful consideration. We have categorised biopsy-naïve men into different risk profiles based on their MRI risk categories and PSAD ranges. We are cognisant that categorisation of continuous variables such as PSAD values is not advisable statistically for creating risk-prediction models, due to the loss of information and power. However, we are not creating a model for biopsy avoidance; instead, we are merely confirming the potential for clinically meaningful inferences as noted by Boesen *et al.* [5] and Falagario *et al.* [6]. Further, justification of PSAD categories comes from their common usage in clinical care guidelines (EAU, NICE) making our present findings practically relevant (Fig. 1). We recognise that some data points have small numbers of patients making the estimates of the risk of significant cancers less reliable.

We also recognise that these data are applicable for a mean ISUP ≥2 prevalence of 35% (range 28–46%) in biopsy-naïve men, and would need to be adjusted to other population prevalence's. Validation of our approach of adapting MRI findings by PSAD values for biopsy decisions is beginning to emerge [11] (Fig. S1b), reinforcing their routine use for biopsy decisions in clinical practice (EAU, NICE), while we wait the validation of MRI-based multivariate risk prediction tools. The proposed approach is hypothesis generating and in need of further prospective validation in different populations of men at risk of prostate cancer.

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Conflict of Interest

None declared.

Ivo G. Schoots[1,2] and Anwar R. Padhani[3]

[1]Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam,, [2]Department of Radiology, Netherlands Cancer Institute, Amsterdam, the Netherlands and [3]Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, Northwood, UK

References

1 **Drost FH**, **Osses DF**, **Nieboer D et al.** Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst Rev* 2019; 4: CD012663

2 **Padhani AR**, **Barentsz J**, **Villeirs G et al.** PI-RADS steering committee: the PI-RADS multiparametric MRI and MRI-directed biopsy pathway. *Radiology* 2019; 292: 464–74

3 **Schoots IG**, **Padhani AR**. Personalizing prostate cancer diagnosis with multivariate risk prediction tools: how should prostate MRI be incorporated? *World J Urol* 2020; 38: 531–45

4 **Schoots IG**, **Roobol MJ**. Multivariate risk prediction tools including MRI for individualized biopsy decision in prostate cancer diagnosis: current status and future directions. *World J Urol* 2020; 38: 517–29

5 **Boesen L**, **Nørgaard N**, **Løgager V et al.** Prebiopsy biparametric magnetic resonance imaging combined with prostate-specific antigen density in detecting and ruling out Gleason 7–10 prostate cancer in biopsy-naive men. *Eur Urol Oncol* 2019; 2: 311–9

6 **Falagario UG**, **Martini A**, **Wajswol E et al.** Avoiding unnecessary magnetic resonance imaging (MRI) and biopsies: negative and positive predictive value of MRI according to prostate-specific antigen density, 4Kscore and risk calculators. *Eur Urol Oncol* 2020; 3: 700–4

7 **Knaapila J**, **Jambor I**, **Perez IM et al.** Prebiopsy IMPROD biparametric magnetic resonance imaging combined with prostate-specific antigen density in the diagnosis of prostate cancer: an external validation study. *Eur Urol Oncol* 2020; 3: 648–56

8 **van der Leest M**, **Cornel E**, **Israel B et al.** Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naive men with elevated prostate-specific antigen: a large prospective multicenter clinical study. *Eur Urol* 2019; 75: 570–8

9 **Hansen NL**, **Barrett T**, **Kesch C et al.** Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naive men with suspicion of prostate cancer. *BJU Int* 2018; 122: 40–9

10 **Thompson IM**, **Pauler DK**, **Goodman PJ et al.** Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. *N Engl J Med* 2004; 350: 2239–46

11 **Stevens E**, **Truong M**, **Bullen JA**, **Ward RD**, **Purysko AS**, **Klein EA**. Clinical utility of PSAD combined with PI-RADS category for the detection of clinically significant prostate cancer. *Urol Oncol* 2020; 38: 846e9–16

Correspondence: Ivo G. Schoots, Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center, P.O. Box 2040, 's-Gravendijkwal 230, 3000 CA, Rotterdam, the Netherlands.

e-mail: i.schoots@erasmusmc.nl

Abbreviations: EAU, European Association of Urology; ISUP, International Society of Urological Pathology; NICE, National Institute for Health and Care Excellence; PI-RADS, Prostate Imaging-Reporting and Data System; PSAD, PSA density.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Study characteristics.
Table S2. Diagnostics metrics for significant prostate cancer detection (ISUP Grade ≥2) at various thresholds of PI-RADS score and PSAD risk category, related to biopsy avoidance.
Fig. S1. Proportions of clinically significant prostate cancer related to PI-RADS and PSAD risk category in biopsy-naïve men.