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Stabile, A.; Dell'Oglio, P.; Cobelli, F. de; Esposito, A.; Gandaglia, G.; Fossati, N.; ... ; Briganti, A.

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Association Between Prostate Imaging Reporting and Data System (PI-RADS) Score for the Index Lesion and Multifocal, Clinically Significant Prostate Cancer

Armando Stabile [a,†,*], *Paolo Dell'Oglio* [a,†], *Francesco De Cobelli* [b], *Antonio Esposito* [b], *Giorgio Gandaglia* [a], *Nicola Fossati* [a], *Giorgio Brembilla* [b], *Giulia Cristel* [b], *Gianpiero Cardone* [c], *Federico Deho'* [a], *Andrea Losa* [d], *Nazareno Suardi* [d], *Franco Gaboardi* [d], *Alessandro Del Maschio* [b], *Francesco Montorsi* [a], *Alberto Briganti* [a]

[a] *Department of Urology and Division of Experimental Oncology, Urological Research Institute, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy;* [b] *Department of Radiology, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy;* [c] *Department of Radiology, IRCCS San Raffaele Turro, Milan, Italy;* [d] *Department of Urology, IRCCS San Raffaele Turro, Milan, Italy*

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Abstract

Background: The ability to identify clinically significant prostate cancer (csPCa) has dramatically improved with the introduction of multiparametric magnetic resonance imaging (mpMRI). Given the growing interest in targeted biopsy and focal therapy, improving our knowledge on the relationship between mpMRI parameters and the ability to predict csPCa multifocality is mandatory.
Objective: To assess whether the Prostate Imaging Reporting and Data System (PI-RADS) score for the index lesion (IL) may predict multifocal csPCa undetected by mpMRI.
Design, setting, and participants: The study included 343 patients who underwent mpMRI of the prostate with subsequent biopsy between 2014 and 2017 at a single tertiary care referral centre.
Intervention: Lesions with a PI-RADS v.2 score $\geq$2 detected at mpMRI (IL) were targeted with a fusion biopsy (Bx) approach (mpMRI-Bx). Moreover, each patient underwent a random extended transrectal ultrasound-guided biopsy (TRUS-Bx) during the same session.
Outcome measurements and statistical analysis: csPCa outside the IL was defined as disease detected at TRUS-Bx with a Gleason score (GS) $\geq$ 3 + 4 and equal to or greater than the GS for the IL. The extent of csPCa detected in target and random cores was reported and stratified according to the GS and PI-RADS score for the IL. The probability of diagnosing csPCa outside the IL according to the PI-RADS score was also assessed in multivariable logistic regression analyses (MVA) after accounting for confounders.
Results and limitations: The detection rate for csPCa outside the IL was 30%. The detection rate for csPCa at TRUS-Bx was 8% for PI-RADS 2, 15% for PI-RADS 3, 36% for PI-RADS 4, and 58% for PI-RADS 5 lesions (p = 0.03). Overall, the median length of

[†] These authors contributed equally to this work.
[*] Corresponding author. Department of Urology and Division of Experimental Oncology, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. Tel.: +39 02 26436923; Fax: +39 02 26437298.
E-mail address: armando.stabile88@gmail.com (A. Stabile).

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csPCa found at TRUS-Bx and thus missed at mpMRI was 2.6 mm. However, the length significantly increased with PI-RADS score for the IL, and was 1.8, 2.3, 2.8, and 3.8 mm for PI-RADS 2, 3, 4, and 5 lesions, respectively ($p = 0.03$). On MVA, PI-RADS 4 (odds ratio [OR] 7.6; $p = 0.008$) and PI-RADS 5 scores (OR 17.3; $p < 0.001$) were independent predictors of the presence of csPCa outside the IL. The study is limited by its retrospective design.

Conclusions: Overall, the accuracy of mpMRI in identifying multifocal csPCa is poor, missing low-volume csPCa in approximately 30% of patients. Moreover, the rate and the extent of csPCa undetected by mpMRI significantly increased with the PI-RADS score for the IL, which can thus be considered a proxy for tumour multifocality.

Patient summary: The accuracy of multiparametric magnetic resonance imaging in identifying prostate cancer multifocality is poor. False negative findings were highly related to the PI-RADS score of the index lesion. These findings raise concerns about the indication for targeting the index lesion only when considering prostate biopsy and focal approaches.

1. Introduction

The widespread use of prostate-specific antigen (PSA) has led to an increase in the diagnosis of localised, low-risk prostate cancer (PCa) [1–3]. In order to reduce such overdiagnosis, novel diagnostic and therapeutic approaches have been developed. Multiparametric magnetic resonance imaging (mpMRI) of the prostate has demonstrated high diagnostic accuracy for clinically significant PCa (csPCa) [4]. For this reason, mpMRI has been included in targeted biopsy strategies, and can increase the detection of csPCa while reducing the rates of insignificant disease relative to systematic transrectal ultrasound-guided biopsy (TRUS-Bx) [5]. Although current guidelines support the use of concurrent systematic biopsy at the time of targeted biopsy, some authors still consider targeted biopsy alone sufficient for the detection of csPCa [6]. Moreover, mpMRI of the prostate is also mandatory for accurate selection of PCa patients who may be candidates for focal therapy. In this context, general consensus has been reached in treating only the mpMRI-detected index lesion (IL) in men suitable for focal therapy [7,8]. The rationale for targeting the IL only with biopsy and focal approaches is the concept that the IL is the driver of prognosis in the majority of PCa patients [9]. However, no prospective study has ever fully confirmed this hypothesis. This issue is key, since other high-grade non-ILs potentially missed by mpMRI may themselves represent a source of systemic dissemination if left untreated using focal approaches. Although previous studies have assessed the risk of csPCa outside the IL, data on the association between IL features and multifocal aggressive PCa are currently scarce [10,11]. Such risk-assessment would be key for proper risk stratification and selection of candidates for focal therapy given the possible non-negligible risk of harbouring csPCa outside the IL, even if smaller in size. We hypothesised that the IL characteristics, in terms of the Prostate Imaging Reporting and Data System (PI-RADS) score, are strictly related to the presence of csPCa outside the IL. Specifically, we hypothesised that higher PI-RADS scores for the IL are associated with a higher probability of harbouring multifocal significant disease. To address this issue, we used data for a contemporary cohort of patients who underwent mpMRI and subsequent mpMRI-Bx in association with TRUS-Bx.

2. Patients and methods

2.1. Study population

The study cohort consisted of 343 consecutive patients who underwent mpMRI of the prostate with subsequent transrectal targeted fusion mpMRI-Bx and concomitant TRUS-Bx at a single tertiary care referral centre between January 2013 and February 2017. Data were prospectively collected from the first case performed.

2.2. mpMRI

All patients underwent a 1.5-T mpMRI study (Achieva and Achieva dStream, Philips Medical Systems, Best, Netherlands) with a phased-array surface coil and an endorectal coil (BPX-15; Bayer Medical Care, Indianola, PA, USA). According to the European Society of Urogenital Radiology guidelines, the imaging protocol consisted of multiplanar T2-weighted images, diffusion-weighted imaging (DWI, with *b* values of 0–800–1400/1600 s/mm^2; apparent diffusion coefficient maps were automatically elaborated), dynamic contrast-enhanced (DCE) MRI, and delayed T1-weighted images with fat suppression. For patients who had previously received one or more sets of biopsies, all mpMRI scans were performed at least 4 wk after prostate biopsy, and precontrast T1-weighted images were recorded to rule out post-biopsy haemorrhagic artefacts. The mpMRI images were scored and reported according to PI-RADS v.2 [12]. Three experienced radiologists analysed the mpMRI findings. Imaged lesions with a PI-RADS v.2 score $\geq$2 detected at mpMRI were targeted. Moreover, all patients regardless of PI-RADS score underwent random biopsy during the same session.

2.3. Prostate biopsy technique and histopathologic examination

A software registration fusion approach was used to biopsy the lesions visualised on mpMRI. In the case of multiple suspicious lesions detected at mpMRI, each lesion was targeted. Each patient also concomitantly underwent a standard 12-core random systematic biopsy (TRUS-Bx)

during the same session, in accordance with the currently available guidelines [13]. Random sampling was performed, avoiding the IL and any other eventual lesions indicated as suspicious by mpMRI and keeping a margin distance of 5 mm. TRUS was performed using a Flex Focus 500 machine with a biplanar transducer (BK Medical, Herlev, Denmark). Fusion biopsies were carried out by three experienced urologists using an 18-gauge needle and a biopsy gun providing a specimen size of 18–22 mm. For software registration fusion, both the prostate and the regions of interest were contoured and superimposed with the TRUS image before biopsy using a BioJet fusion system (D&K Technologies, Barum, Germany) [14]. Technical data and use of the BioJet fusion system have been previously described [15]. All prostate biopsy specimens were analysed by two dedicated uropathologists.

2.4. Variable definition

Complete clinical data consisting of age at biopsy, PSA (ng/ml), prostate volume defined at TRUS (ml), PI-RADS score (2 vs 3 vs 4 vs 5), number of targeted cores per MRI lesion, volume of the IL (calculated using PACS software after manually contouring each IL axial slice on T2-weighted imaging), number of random cores, length of PCa (mm) in each core, and previous biopsy history (none vs previous negative) were available for all patients. The primary and secondary Gleason score (GS) were available separately for all cores taken at mpMRI-Bx and TRUS-Bx. The median length of cancer within random and targeted cores was calculated as the average cancer involvement in the cores. The IL is the lesion with the highest PI-RADS assessment category or, alternatively, the largest lesion if there is more than one in the same category [12].

2.5. Outcome

The aim of our study was to evaluate the relationship between mpMRI data, namely the PI-RADS score, and the presence of csPCa outside the mpMRI-detected IL. Non-IL csPCa was defined as a lesion detected at random biopsy (TRUS-Bx) with GS $\geq$7 and equal to or greater than the GS for the IL.

2.6. Statistical analysis

Our statistical analysis consisted of four steps. First, the median and interquartile range and the frequency and proportion were reported for continuous and categorical variables, respectively. A Mann-Whitney *U* test and a χ^2 test were applied to determine the statistical significance of differences in medians and proportions, respectively.

Second, the detection rate for PCa was reported according to PI-RADS score and lesion location. csPCa locations were reported according to a standard scheme for sextant biopsy, dividing the prostate into the left and right base, mid, and apex [16]. The same scheme was used to report the location of mpMRI-detected lesions. The length of csPCa detected in target and random cores was reported and stratified according to GS and PI-RADS score for the IL.

Third, multivariable logistic regression analyses were performed to identify predictors of the presence of csPCa outside the mpMRI-detected IL. Covariates included age at biopsy, PSA, prostate volume, PI-RADS score (2 vs 3 vs 4 vs 5), previous biopsy history (none vs negative), and number of random cores taken at TRUS-Bx.

Fourth, the multivariable relationship between PI-RADS score and the presence of csPCa outside the mpMRI-detected IL was graphically plotted after accounting for the same confounders included in the logistic model.

Finally, the same analyses were repeated for the biopsy-naïve and previous negative biopsy subgroups.

All statistical tests were performed using the RStudio graphical interface v.0.98 for R v.3.0.2 (R Foundation, Vienna, Austria). All tests were two-sided with the significance level set at $p < 0.05$.

Table 1 – Descriptive characteristics of 343 patients undergoing mpMRI of the prostate with subsequent targeted and concomitant systematic biopsy at a single tertiary care referral centre between 2014 and 2017.

Variable	Overall (*n* = 343)	Biopsy-naïve (*n* = 186, 54.2%)	Previous negative biopsy (*n* = 157, 45.8%)	*p* value
Median age at biopsy, yr (IQR)	66 (59–72)	65 (59–71)	67 (60–73)	0.2
Median PSA, ng/ml (IQR)	6.9 (4.5–10)	6 (4.2–8.6)	7.7 (5.0–11.1)	0.001
Median prostate volume, ml (IQR)	45 (36–63)	45 (36–65)	47 (36–62)	0.9
PI-RADS score, *n* (%)				
2	25 (7.3)	15 (8.1)	9 (5.7)	
3	118 (34.4)	67 (36.0)	51 (32.5)	0.36
4	145 (42.3)	72 (38.7)	74 (47.1)	
5	55 (16.0)	32 (17.2)	23 (14.6)	
Median targeted cores per MRI lesion, *n* (IQR)	3 (2–3)	3 (2–3)	3 (2–4)	0.54
Median random cores, *n* (IQR)	12 (8–12)	12 (8–12)	12 (7–12)	0.18
Median IL volume, ml (range)	0.7 (0.4–1.4)	0.6 (0.4–1.4)	0.7 (0.4–1.4)	0.8
Overall detection of PCa, *n* (%)				
No	119 (34.7)	68 (36.6)	51 (32.5)	0.5
Yes	224 (65.3)	118 (63.4)	106 (67.5)	
Overall detection of csPCa, *n* (%)				
No	158 (46.7)	88 (47.3)	69 (43.9)	0.54
Yes	185 (53.3)	98 (52.3)	88 (56.1)	
csPCa detection in targeted cores, *n* (%)				0.92
No	175 (51.0)	98 (52.7)	70 (49.0)	
Yes	168 (49.0)	88 (47.3)	80 (51.0)	
csPCa detection in random cores, *n* (%)				0.03
No	219 (63.8)	109 (58.6)	110 (70.1)	
Yes	124 (36.2)	77 (41.4)	47 (29.9)	
csPCa detection in random cores with GS $\geq$ IL GS, *n* (%)				0.04
No	239 (69.7)	121 (46.3)	118 (75.2)	
Yes	104 (30.3)	65 (53.7)	39 (24.8)	

IQR = interquartile range; PCa = prostate cancer; csPCa = clinically significant PCa; mpMRI = multiparametric magnetic resonance imaging; IL = index lesion.

Table 2 – PCa detection rates stratified according to the PI-RADS score for the IL.

Variable	PI-RADS 2 (*n* = 25, 7.3%)	PI-RADS 3 (*n* = 118, 34.4%)	PI-RADS 4 (*n* = 145, 42.3%)	PI-RADS 5 (*n* = 55, 16%)	*p* value
Overall detection of PCa, *n* (%)					
No	19 (76)	60 (50.9)	37 (25.5)	3 (5.5)	<0.001
Yes	6 (24)	58 (49.1)	108 (74.5)	52 (94.5)	
Detection of csPCa, *n* (%)					
Overall					<0.001
No	21 (84)	80 (67.8)	52 (35.9)	5 (9.1)	
Yes	4 (16)	38 (32.2)	93 (64.1)	50 (90.1)	
In target cores					
No	22 (88)	88 (74.6)	59 (40.7)	6 (10.9)	<0.001
Yes	3 (12)	30 (25.4)	86 (59.3)	49 (89.1)	
In random cores					<0.001
No	22 (88)	93 (78.8)	83 (57.2)	21 (38.2)	
Yes	3 (12)	25 (21.2)	62 (42.8)	34 (61.8)	
In random cores with GS ≥ IL GS					<0.001
No	23 (92)	100 (84.7)	93 (64.1)	23 (41.8)	
Yes	2 (8)	18 (15.2)	52 (35.9)	32 (58.2)	

PI-RADS = Prostate Imaging Data and Reporting System; PCa = prostate cancer; csPCa = clinically significant PCa; IL = index lesion; GS = Gleason score.

3. Results

Descriptive characteristics of the patient population are reported in Table 1. Among the study population, 186 men (54.2%) were biopsy-naïve, while 157 (45.8%) had undergone at least one previous negative biopsy.

The overall PCa detection rate was 48% for TRUS-Bx and 55% for mpMRI-Bx ($p = 0.09$), while the csPCa detection rate was 36.2% for TRUS-Bx and49% for mpMRI-Bx ($p < 0.001$). The csPCa detection rate in random cores with a GS equal to or higher than the GS for the IL was 30%. The detection rates according to PI-RADS score are reported in Table 2. The csPCa detection rate for TRUS-Bx with GS equal to or higher than the GS for the IL increased with IL PI-RADS score: 8% for PI-RADS 2, 15.2% for PI-RADS 3, 35.9% for PI-RADS 4, and 58.2% for PI-RADS 5 lesions ($p = 0.03$).

Overall, 290 sextants were positive for csPCa at TRUS-Bx (Table 3). Moreover, of the sextants missed at mpMRI, 76% (150/173), 88% (66/75) and 94.8% (74/78) with GS 3 + 4, 4 + 3, and ≥8, respectively, had GS equal to or higher than the GS for the IL. The majority (36.5%) of these csPCa lesions missed at mpMRI were located within the middle part of the prostate. In addition, 32.7% (34/104) of patients diagnosed with csPCa in random cores with GS equal to or higher than the GS for the IL had bilateral disease.

Overall, the median length of csPCa found in targeted and random cores was 6.0 and 2.6 mm, respectively (Table 4). When stratifying according to GS, the median length of csPCa in targeted cores was 6, 8, and 7.5 mm for GS 7, 8, and ≥9, respectively ($p = 0.06$). In random cores the median length of csPCa with GS equal to or higher than the GS for the IL was 3, 4.7, and 2.3 mm for GS 7, 8, and ≥ 9, respectively (Table 4; $p = 0.1$). The median length of csPCa found in random cores significantly increased with the PI-RADS score, at 1.8, 2.3, 2.8, and 3.8 mm for PI-RADS 2, 3, 4, and 5 lesions, respectively ($p = 0.03$). The rate of contralateral csPCa found in random cores with GS equal to or higher than the GS for the IL was 50.0%, 44.4%, 55.8%, and 59.4% for PI-RADS 2, 3, 4, and 5 lesions, respectively (Table 4; $p = 0.7$).

On multivariable logistic regression analysis, the presence of mpMRI IL scored as PI-RADS 4 (odds ratio [OR] 7.6, 95% confidence interval [CI] 2.4–31.2; $p = 0.008$) or PI-RADS 5 (OR 17.3, 95% CI 4.3–59; $p < 0.001$) was significantly associated with the presence of csPCa outside the IL (Table 5). Furthermore, prostate volume (OR 0.98 per cm^3, 95% CI 0.97–0.99; $p = 0.003$), age (OR 1.05 per year, 95% CI 1.01–1.08; $p = 0.009$), a previous negative biopsy (OR 0.54, 95% CI 0.3–0.9; $p = 0.02$) and the number of random cores (OR 1.15 per single core, 95% CI 1.06–1.25; $p < 0.001$) were also independent predictors of csPCa (Table 5).

Table 3 – Distribution of csPCa with GS equal to or higher than the GS for the index lesion detected at systematic random biopsy according to sextants.

Gleason score	Cancers, *n* (%) [a]						
	Right apex	Left apex	Right middle	Left middle	Right base	Left base	Total
3 + 4	27 (9.3)	23 (7.9)	29 (10)	25 (8.6)	25 (8.6)	21 (7.2)	150 (51.7)
4 + 3	9 (3.1)	14 (4.8)	7 (2.4)	19 (6.6)	6 (2.1)	11 (3.8)	66 (22.8)
4 + 4 or 3 + 5 or 5 + 3	7 (2.4)	6 (2.1)	9 (3.1)	5 (1.7)	6 (2.1)	5 (1.7)	38 (13.1)
4 + 5 or 5 + 4 or 5 + 5	6 (2.1)	6 (2.1)	7 (2.4)	5 (1.7)	7 (2.4)	5 (1.7)	36 (12.4)
Total	49 (16.9)	49 (16.9)	52 (17.9)	54 (18.6)	44 (15.2)	42 (14.5)	290 (100)

csPCa = clinically significant prostate cancer; GS = Gleason score.
[a] Percentage of the total of sextants positive for csPCa with GS equal or greater than GS for the index lesion.

Table 4 – Characteristics of csPCa in positive targeted and random cores stratified according to GS and PI-RADS score for the index lesion.

Variable	Overall csPCa	GS 7	GS 8	GS ≥9	*p* value
Median PCa length, mm (IQR)					
In positive random cores	2.6 (1.3–5.2)	3 (1.5–5.3)	4.7 (3–8.9)	2.3 (1.6–4.4)	0.1
In positive targeted cores	6 (3–9)	6 (4–9)	8 (5.8–10.5)	7.5 (4.6–11.9)	0.06
Median no. of positive cores, *n* (IQR)					
Random cores	3 (2–4.2)	3 (2–4)	3 (1–5)	4 (3–6)	0.74
Targeted cores	3 (1–4)	3 (2–4)	3 (2–4)	3 (3–4)	0.45
	PI-RADS 2	PI-RADS 3	PI-RADS 4	PI-RADS 5	*p* value
Median PCa length, mm (IQR)					
In positive random cores	1.8 (1.6–5.5)	2.3 (1.3–2.4)	2.8 (1.7–5.1)	3.8 (2.0–6.5)	0.03
In positive targeted cores	7.9 (7.7–8.1)	5.0 (1.6–9.0)	6.0 (3.4–8.0)	9.4 (6.2–11.5)	0.002
Contralateral PCa, *n* (%)					
No	1 (50)	10 (55.6)	23 (44.2)	13 (40.6)	0.7
Yes	1 (50)	8 (44.4)	29 (55.8)	19 (59.4)	

PCa = prostate cancer; csPCa = clinically significant PCa; GS = Gleason score; PI-RADS = Prostate Imaging Data and Reporting System.

Figure 1 shows the relationship between PI-RADS score for the IL and the probability of detecting csPCa outside the IL after accounting for the mentioned confounders. We observed a progressive increase in the probability of diagnosing csPCa outside the IL detected at mpMRI with increasing PI-RADS score, ranging from approximately 10% for PI-RADS 2 lesions to ~70% for PI-RADS 5 lesions.

Similar findings were observed for subgroup analyses focusing on biopsy-naïve patients (Supplementary Table 1). Specifically, an mpMRI-detected IL scored as PI-RADS 4 (OR 9.6, 95% CI 1.7–45.8; $p = 0.03$) or PI-RADS 5 (OR 21.4, 95% CI 4.6–67; $p = 0.003$) and age (OR 1.05 per year, 95% CI 1.01–1.08; $p = 0.03$) were significantly associated with the presence of csPCa outside the IL. Conversely, among men with a previous negative biopsy, mpMRI-detected ILs scored as PI-RADS 4 or PI-RADS 5 were not independent predictors of csPCa outside the IL (Supplementary Table 2). The multivariate associations between the PI-RADS score and the probability of detecting csPCa outside the IL are depicted in Supplementary Figures 1 and 2 for the biopsy-naïve and previous negative biopsy patients, respectively.

Table 5 – Multivariable logistic regression model predicting csPCa outside the index lesion in 343 patients undergoing mpMRI of the prostate with subsequent targeted and concomitant systematic biopsy performed at a single tertiary care referral centre between 2014 and 2017.

Predictor	Multivariable analysis	
	OR (95% CI)	*p* value
Age	1.05 (1.01–1.08)	0.009
Prostate-specific antigen	1.01 (0.9–1.03)	0.3
Prostate volume [a]	0.98 (0.97–0.99)	0.003
PI-RADS score		
2	Reference	–
3	2.5 (0.64–10.3)	0.2
4	7.6 (2.4–31.2)	0.008
5	17.3 (4.3–59)	<0.001
Previous biopsy		
Biopsy-naïve	Reference	–
Previous negative biopsy	0.54 (0.3–0.9)	0.02
Number of random cores	1.15 (1.06–1.25)	<0.001

csPCa = clinically significant prostate cancer; mpMRI = multiparametric magnetic resonance imaging; OR = odds ratio; CI = confidence interval; PI-RADS = Prostate Imaging Data and Reporting System.
[a] Prostate volume assessed at transrectal ultrasonography.

4. Discussion

mpMRI represents a useful tool that can improve the management of patients with PCa in terms of diagnosis, staging, and outcomes [17,18]. Given its high sensitivity and accuracy in detecting csPCa, mpMRI is increasingly used in selecting optimal candidates not only for prostate biopsy but also for focal therapy. However, even if an IL is found at mpMRI, concerns have been raised about the diagnostic ability of mpMRI for low-volume, high-grade PCa foci outside the IL [19]. Despite these concerns, general consensus has been reached to extend the indication for focal therapy to: (1) unifocal intermediate- to high-risk disease with an mpMRI-detected IL regardless of the PI-RADS score; and (2) multifocal PCa but with a single mpMRI-detected lesion [7]. Such a shift is mainly based on the hypothesis that most metastatic PCa arises from the cell clone of the single dominant lesion in terms of grade and size [9]. Although this hypothesis may be considered reasonable, it is mainly limited by the lack of a well-performed prospective validation. Therefore, it is possible that even smaller lesions with the same or even higher grade than the IL may be potential sources of metastatic spread. However, these lesions would remain untreated in the case of IL-only ablation. In this context, only a few studies have assessed the relationship between mpMRI data and the focality of PCa, and provided controversial results [10,11,19]. Moreover, none of the studies assessed the relationship between the characteristics of the mpMRI-detected IL, namely the PI-RADS score, and the presence of csPCa outside the IL. In this light, we hypothesised that the PI-RADS score for the IL is strictly related to the presence of csPCa outside the IL, and thus to multifocal high-grade disease. The latter was defined as lesion(s) undetected by mpMRI with GS of least 3 + 4 and equal to or higher than the GS for the IL. This definition was used since it is currently under debate whether to consider as clinically meaningful a PCa focus found outside of the IL if either of low grade or of lower grade than the IL. Therefore,

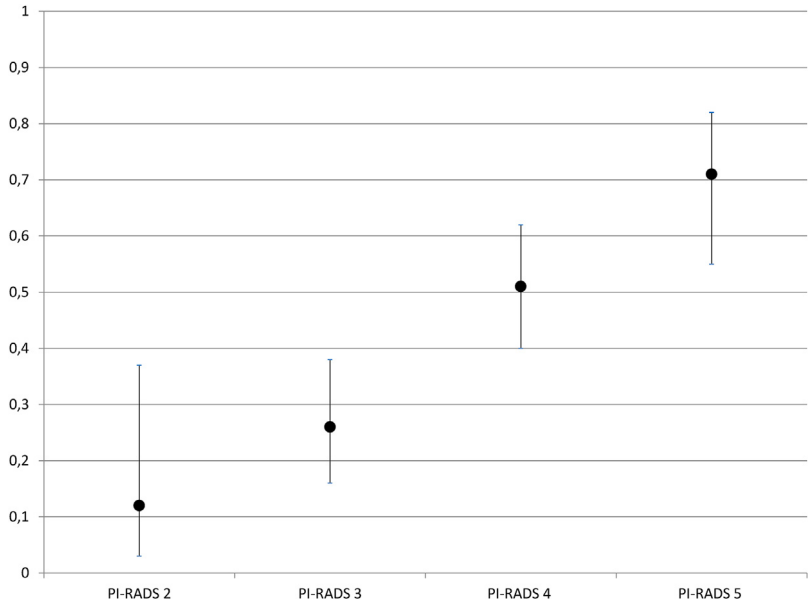

Fig. 1 – Relationship between Prostate Imaging Reporting and Data System (PI-RADS) score and the probability of diagnosing clinically significant prostate cancer (csPCa) outside the index lesion. csPCa was defined as Gleason score at biopsy of ≥7 in random cores and equal to or greater than the Gleason score for PCa diagnosed within the index lesion.

we focused exclusively on lesions missed by mpMRI that were at least of the same grade as the IL.

Several results of our study are noteworthy. First, we observed that mpMRI missed a significant number of small-volume csPCas. Specifically, the detection rate for csPCa in random cores with GS equal to or higher than GS for the IL was 30%. Interestingly, this detection rate increased with the PI-RADS score, ranging from 8% to 58% for PI-RADS 2 and PI-RADS 5 mpMRI-detected ILs, respectively (Table 2). These results were even more evident when accounting for confounders. When we assessed the multivariable relationship between the IL PI-RADS score and the probability of diagnosing multifocal csPCa (of equal or higher grade than the IL) we found a 50% and 70% risk of high-grade disease not detected by mpMRI in men with PI-RADS 4 and 5 scores, respectively (Fig. 1). On multivariable analyses, patients with PI-RADS 4 and 5 scores had approximately eight- and 17-fold higher risk, respectively, of harbouring csPCa outside the IL when compared with men with a PI-RADS 2 score ($p = 0.008$ and $p < 0.001$, respectively). Conversely, it is of note that the presence of an IL classified as PI-RADS 3 failed to reach independent predictor status. Taken together, all these finding suggest that the PI-RADS score is strictly related to the multifocal nature of csPCa. To the best of our knowledge, we are the first to test this relationship. Few available studies have assessed the association between mpMRI and PCa multifocality, and these used different methodology and yielded discordant findings [10,11]. For example, Okamura et al. [10] reported that in a series of 37 men who underwent mpMRI before radical prostatectomy (RP), mpMRI was not useful in the case of multifocal disease. Conversely, Delongchamps et al. [11] reported mpMRI sensitivity of 80% for detection of bilateral disease. Le et al. [19] observed that 20% of 122 men who underwent mpMRI before RP had csPCa within non-ILs, and almost all of these were missed by mpMRI. However, none of these studies correlated the IL PI-RADS score with csPCa multifocality using our approach.

Second, although mpMRI missed several foci of csPCa outside the IL, these were of lower volume. In particular, the average length of csPCa involvement was lower in random cores than in targeted cores (2.6 vs 6.0 mm; $p < 0.001$). This difference was observed for csPCa of all GSs (Table 4). These findings suggest that mpMRI still missed csPCa, but overall these foci were small in size and not extensive. However, whether these high-grade small tumour foci are unable to metastasise and are thus of lower relevance than the IL has yet to be demonstrated. Moreover, after stratification of the extent of csPCa involvement in random cores according to the PI-RADS score, we observed a trend towards a higher tumour burden outside the IL with increasing PI-RADS score. In addition, the higher the PI-RADS score, the higher was the probability of finding contralateral csPCa (Table 4). Therefore, although tumours missed by mpMRI were small overall, the size and extent of these foci were highly related to the IL PI-RADS score. For example, men with a PI-RADS 5 IL had a median length of missed csPCa of approximately 4 mm in random cores and their rate of bilateral disease was 60%.

Third, the distribution of csPCa missed at mpMRI was quite regular, with a similar detection rate for each sextant (Table 3). Our findings differ from those reported by Schouten et al. [20], who found that mpMRI-Bx most often missed lesions located in dorsolateral and apical segments. Moreover, it is noteworthy that 32.7% (34/104) of patients diagnosed with csPCa in random cores with GS equal to or higher than the GS for the IL had bilateral disease. All these missed sextants must be considered as mpMRI false negatives and must be taken into account during the

decision-making process for prostate biopsy and focal therapy, especially given the high rate of bilateral significant disease reported, since hemiablation is the most popular technique for focal treatment [21].

Fourth, we provided additional evidence that the number of random cores was significantly associated with csPCa outside the IL. This finding overwhelmingly confirms the need for random extended prostate sampling biopsy in addition to random biopsy. Several studies have already provided evidence that random biopsy combined with targeted biopsy yields the highest accuracy in terms of detection of csPCa and csPCa foci [22–24]. This is the approach currently supported by virtually all the guidelines [13,22]. In this context, the most recent consensus conference on focal therapy agreed that in MRI-negative areas, systematic biopsies remain necessary even if an MRI-suspicious lesion has already been sampled using mpMRI-Bx [8]. So far, no agreement has been reached on the type and extent of biopsy for MRI-negative areas [8]. Our results support the use of mpMRI-Bx in combination with TRUS-Bx in selecting patients for focal therapy, and discourage use of the former alone.

Lastly, it is of note that the detection rates for both PCa and csPCa were higher in the previous negative biopsy group than in the biopsy-naïve group. However, we failed to observe a statistically significant difference between the two groups (Table 1). The cancer detection rate observed in the previous negative biopsy group is even higher when compared with previous published series. For example, Filson et al. [23] reported csPCa detection rates of 42.5% for biopsy-naïve men and 26.4% for men with a previous negative biopsy in a cohort of patients who underwent both TRUS-Bx and mpMRI-Bx. The main factor that might explain these differences is the higher proportion of PI-RADS scores $\geq$4 in our group with a previous negative biopsy (62%) in comparison with the cohort of Filson et al. (30%). However, we observed quite similar PI-RADS score distributions for the biopsy-naïve and previous negative biopsy groups ($p = 0.36$), which might explain the similar rates of PCa detected in the two groups. Interestingly, the rate of csPCa detection in targeted cores was similar between the biopsy-naïve and previous negative biopsy groups ($p = 0.92$; Table 1). However, the difference between the two groups was significant for random cores ($p = 0.03$; Table 1). This might be related to the weaker correlation between the PI-RADS score and multifocality of csPCa among patients with a previous negative biopsy, as supported by the multivariable logistic regression analysis predicting the presence of csPCa in the overall population (Table 5). Indeed, we observed that the presence of at least one previous negative biopsy was negatively related to the probability of detecting csPCa outside the IL. In this context, when we assessed the multivariable correlation between the IL PI-RADS score and the probability of diagnosing multifocal csPCa in the biopsy-naïve and previous negative biopsy groups, PI-RADS 4 and 5 lesions were significantly related to csPCa multifocality in the former group (OR 9.6 and 21.4, respectively; $p \leq 0.03$) but not in the latter. The relationship between the IL PI-RADS score and the probability of detecting csPCa outside the IL is clear and sharp for the biopsy-naïve cohort but was not present for men with a previous negative biopsy. These differences in the correlation between the IL PI-RADS score and csPCa multifocality are depicted in graphical representations of the multivariable logistic regression analyses performed for the two subgroups in Supplementary Figures 1 and 2.

Taken together, our findings question the ability of mpMRI to detect low-volume, high-grade lesions, especially in men with higher PI-RADS scores. In these cases, the risk of leaving PCa foci of equal or even higher grade than the IL is in the range 55–75%. In an era in which it is still unknown whether these high-grade smaller foci can contribute to patient prognosis, it seems at least questionable to perform IL ablation only, as currently suggested [8].

Despite its strengths, our study is not devoid of limitations. First, our findings originated from a single-centre series. As a consequence, they should be externally validated before being considered generalisable. Second, data regarding RP specimens were not available owing to a lack of information regarding PCa foci and concordance with mpMRI findings in the histology report currently used in our institute. Future prospective studies might fill this gap. Third, our results are based on the use of 1.5-T mpMRI performed with both a phased array surface and an endorectal coil. Since mpMRI at 3.0 T is increasingly used for routine clinical examinations, one might argue that our results could be considered as not reliable. Whether or not mpMRI at 3 T is superior to 1.5 T is still a controversial topic. Nonetheless, several studies [25–27] reported the same accuracy for the two methods in terms of local staging, cancer localisation, and PI-RADS scoring. Moreover, 1.5-T mpMRI performed with both surface and endorectal coils seems to be superior in image quality and tumour delineation when compared with 3-T mpMRI [25–27]. Thus, our findings are reliable, although further prospective studies with different field strengths might clarify and support their generalisability. Finally, we did not account for the number of urologists who performed the biopsies and the number of radiologists who interpreted the mpMRI findings. This may have introduced a bias, although all MRI studies were prospectively performed and collected at a single centre by three expert uroradiologists. Despite these limitations, our study is the first attempt to stratify the risk of multifocal high-risk PCa according to imaging at diagnosis with the ultimate aim of improving patient risk assessment and tailoring the optimal treatment approach.

5. Conclusions

We provided evidence that the accuracy of mpMRI in identifying PCa multifocality is poor. Indeed, mpMRI missed small-volume csPCa outside the IL in approximately one-third of men. Such false negative findings were highly related to the PI-RADS score for the IL. These findings raise concerns about the indication of targeting the IL only, especially for higher PI-RADS scores, given the uncertain metastatic potential of small-volume foci of high-grade PCa. Moreover, our results support the importance of correct, extensive biopsy sampling for accurate patient risk assessment and to tailor the optimal clinical decision-making process.

Author contributions: Armando Stabile had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Briganti, Stabile, Dell'Oglio, Montorsi.
Acquisition of data: Stabile, Dell'Oglio, Gandaglia, Brembilla, Cristel, Suardi, Cardone, De Cobelli.
Analysis and interpretation of data: Stabile, Dell'Oglio, Briganti, Deho', Suardi, Esposito.
Drafting of the manuscript: Stabile, Briganti, Dell'Oglio, Montorsi.
Critical revision of the manuscript for important intellectual content: Stabile, Dell'Oglio, Gandaglia, Brembilla, Cristel, Fossati, Deho', Suardi, Losa, Gaboardi, Cardone, Esposito, De Cobelli, Del Maschio, Montorsi, Briganti.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.euo.2018.01.002.

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