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1 **Diagnostic pathway with multiparametric magnetic resonance imaging vs. standard pathway: Results**
2 **from a randomized prospective study in biopsy-naïve patients with suspected prostate cancer**

3

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26

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30 **ABSTRACT**

31 **Background:** An approach based on multiparametric magnetic resonance imaging (mp-MRI) might increase
32 the detection rate (DR) of clinically significant (cs) prostate cancer (PCa).

33 **Objective:** To compare an mp-MRI-based pathway with the standard approach for the detection of PCa and
34 csPCa.

35 **Design, setting, participants:** Between 11/2014 and 04/2016, 212 biopsy-naïve patients with suspected PCa
36 (PSA \leq 15 ng/ml, negative DRE) were included in the present RCT. Patients were randomized into a prebiopsy
37 mp-MRI group (arm A, 107pts) or a standard biopsy (SB) group (arm B, 105pts).

38 **Intervention:** In arm A, patients with mp-MRI evidence of lesions suspected for PCa were submitted to mp-
39 MRI/TRUS fusion software-guided targeted biopsy (TB) (81pts). The remaining patients in arm A (26pts)
40 with negative mp-MRI and patients in arm B underwent 12-core SB.

41 **Outcomes measurements and statistical analysis:** Primary endpoint: to compare the DR of PCa and csPCa
42 between the two arms of the study; Secondary endpoint: to compare the DR between TB and SB.

43 **Results and limitations:** The overall DRs for PCa (50.5% vs. 29.5%, A vs. B, p=0.002) and csPCa (43.9% vs.
44 18.1%, A vs. B, p<0.001) were higher in arm A. Concerning the biopsy approach, the overall DRs of PCa
45 (60.5% vs. 19.2% vs. 29.5%, p<0.001) and csPCa (56.8% vs. 3.8% vs. 18.1%, p<0.001) were significantly
46 different (TB in arm A, SB in arm A, and SB in arm B, respectively). The reproducibility of the study could
47 have been affected by the single-centre nature.

48 **Conclusion:** A diagnostic pathway based on mp-MRI had a higher DR than the standard pathway in both
49 PCa and csPCa.

50 **Patient summary:** In this randomized trial, we compared a pathway for the diagnosis of prostate cancer,
51 based on multiparametric magnetic resonance imaging, with the standard pathway, based on random
52 biopsy. We found that the mp-MRI-based pathway had better performance than the standard.

53 **INTRODUCTION**

54 Prostate biopsy with multiple samples using a standardized template (standard biopsy - SB) under
55 transrectal ultrasound (TRUS) guidance is the standard diagnostic approach today in suspicion of prostate
56 cancer (PCa)[1], as recommended by the European Urological Association guidelines[2].

57 However, many biopsies are unnecessary, or they cannot detect clinically significant (cs) PCa[3]. With the
58 introduction of the multiparametric prostate MRI (mp-MRI), many authors have reported improved PCa
59 detection and localization[4,5]. Moreover, mp-MRI can be useful to select patients more effectively who
60 are eligible for prostate biopsy because of its high negative predictive value, mainly in men with previous
61 negative mapping[6,7]. Finally, mp-MRI allows the clinician to guide prostate biopsy sampling. Some studies
62 have reported comparable findings of PCa detection rates between mp-MRI targeted biopsies and SB[8,9];
63 however, the latter approach has been described as increasing csPCa detection in biopsy-naïve patients,
64 thus decreasing the detection of non-significant PCa[10].

65 The aim of this randomized, prospective, two-arm study was to evaluate the diagnostic accuracy of the mp-
66 MRI pathway itself and in comparison to the standard pathway in biopsy-naïve men.

67 **MATERIALS AND METHODS**

68 **Study population and design**

69 The study enrolment lasted from 11/2014 to 03/2016. It was conducted in accordance with Good Clinical
70 Practice Guidelines and the ethical principles of the Declaration of Helsinki, as amended in Hong Kong. In
71 addition, the study was approved by the local ethics committee (San Luigi Gonzaga Hospital, Orbassano,
72 Italy). The CONSORT flow diagram is shown in Figure 1.

73 The eligibility criteria were: (1) age ≤ 75 years old; (2) prostate-specific antigen (PSA) **level up to 15 ng/ml**;
74 (3) negative digital rectal examination (DRE); and (4) signed informed consent.

75 The exclusion criteria were: (1) previous prostate biopsy/surgery; (2) previous prostate mp-MRI; and (3)
76 contraindication to mp-MRI.

77 We emphasize that none of the enrolled patients had previously been included in published cohorts.

78 Two-hundred-twenty-three eligible patients scheduled for prostate biopsy in our department were
79 randomly assigned to one of the following arms: arm A, mp-MRI prior to prostate biopsy; or arm B,
80 standard prostate biopsy. In arm A, all patients with mp-MRI evidence of lesions suspicious for PCa were
81 submitted to mp-MRI/TRUS fusion software-based targeted biopsy (TB) (sub-arm A MRI+). In cases of
82 negative mp-MRI, arm A patients underwent SB (sub-arm A MRI-).

83 The present RCT compared the outcomes between the two arms.

84 The primary endpoint was the comparison of the overall detection rates of PCa and csPCa between arm A
85 and B. The secondary endpoints were: (1) comparison of the overall detection rates of PCa and csPCa
86 between sub-arm A MRI+ and MRI-; (2) comparison in terms of pathological results; (3) comparison of
87 complication rates; and (4) follow-up of patients in sub-arm A MRI- and sub-arm A MRI+ with negative
88 biopsy.

89 In this first report, the primary endpoint and the first two secondary endpoints were reached and
90 considered. The study is ongoing to determine to the remaining secondary endpoints.

91 **Randomization**

92 Immediately after signing a specific informed consent form, the patients were randomized into either arm
93 A or B.

94 **Sequence generation: Patients were randomly assigned to arm A or B following a 1:1 simple**
95 **randomization procedure, according to a computer-generated randomization list. The**
96 **randomization list was prepared by an external randomization manager. We emphasize that he**
97 **was the only person to have possession of the list, and he had no clinical involvement in the**
98 **trial.**

99 **Allocation concealment and implementation: Different staff members (blinded to the**
100 **randomization sequence) evaluated the inclusion criteria and obtained the patients' informed**
101 **consents. Immediately after this phase, staff members contacted the external randomization**
102 **manager, who assigned the patients to one of the two groups.**

103 **Finally, independent staff members (F.M. and M.M.) planned the two different diagnostic**
104 **pathways, i.e., mp-MRI and different prostate biopsies in arm A vs. the standard prostate**
105 **biopsies in arm B.**
106

107 **Multiparametric MRI**

108 All of the patients in arm A underwent mp-MRI according to the ESUR guidelines. The PIRADS classification
109 was used to describe the found lesions[11]. mp-MRI was performed out at three centres with a 1.5-T
110 scanner using a 32-channel phase array coil or 4-channel phase array coil combined with an endorectal coil.
111 A description of mp-MRI acquisition is provided in the supplementary material[5,11,12]. Three experienced
112 radiologists analysed the mp-MRI findings. PIRADS_{≥3} lesions were considered suspicious for PCa.

113 **Prostate biopsy**

114 All of the patients underwent prostate biopsy in an ambulatory setting according to the guidelines[2]. TRUS
115 was performed by using a Hawk Ultrasound scanner 2102 EXL with a biplanar transducer (B-K Medical,
116 Herlev, Denmark). Biopsies were performed using a disposable 18-G biopsy gun with a specimen size of 18-
117 22 mm (Bard Medical, Covington, USA) by two dedicated senior urologists. Both of the urologists had a
118 level of experience in SB of >20 years and in TB of >1 year (>100 procedures per urologist).

119 TB was performed by using the BioJet™ fusion system (D&K Technologies, Barum, Germany), as previously
120 described[13]. The gland and the regions of interest (ROIs) were contoured, and the prostate contour was
121 fused in real time with the TRUS image. Biopsies were performed via either a transrectal (55 patients,
122 67.9%) or transperineal (26 patients, 32.1%) approach, based on the location of the ROI: transrectal for
123 ROIs in the peripheral zone; and transperineal for ROIs in the transition, central or anterior zone. The
124 patient was placed in the lithotomy position. TB was performed on a maximum of two ROIs, and three to
125 six cores were obtained for biopsy from each lesion. Lesions from the transition or central zone scored as
126 PIRADS 3 were not biopsied.

127 Twelve-core SB was performed according to the Rodríguez-Covarrubias protocol via a transrectal
128 approach[14].

129 **Pathological analysis**

130 Histopathological examination was conducted by a dedicated uropathologist who was blinded to the
131 inclusion of each patient in the RCT and to the mp-MRI results, according to a standardized protocol[15].

132 The biopsy Gleason score (GS), number of total and positive cores, total and maximum cancer core length
133 (CCL), and maximum cancer core involvement (CCI) rate were recorded according to the standards of
134 reporting for MRI-targeted biopsy studies (START) criteria[16].

135 csPCa was defined according to previously published studies: the START criteria for TB (biopsy GS_{≥7} or
136 maximum CCL_{≥5}mm[16,17]); and the updated Epstein criteria for SB[18].

137 **Sample size determination and statistical analyses**

138 A sample size of 186 patients (93 per arm) was required to detect a 20% absolute increase (from 30% to
139 50% with arm B vs. arm A, respectively) in the detection rate of PCa, with an alpha error of 0.05 and a beta
140 error of 0.20 (two-sample test for proportions, superiority design). Considering 10% of patients lost to

141 follow-up, the total sample size was calculated to number 205 patients. No interim analyses were planned,
142 while all procedures were performed on an intention-to-treat basis.

143 The associations between categorical variables (PIRADS and GS) and the arm were analysed by Fisher's
144 exact test; the Mann-Whitney and Kruskal-Wallis tests were used for continuous variables. All of the results
145 for continuous variables are expressed as the median (inter-quartile rate [IQR]). All of the reported p-values
146 were obtained by the two-sided exact method at the conventional 5% significance level. Data were
147 analysed as of April 2016 by R software, version 3.2.3 (R Foundation for Statistical Computing, Vienna-A,
148 <http://www.R-project.org>), **according to previously published guidelines for the reporting of statistics[19].**

149 **RESULTS**

150 Totals of 111 and 112 patients were enrolled in arms A and B, respectively. Protocol violations were
151 registered in 4 of 111 patients (3.6%) and 7 of 112 patients (6.3%) in arms A and B, respectively. After
152 exclusion of these patients, 107 and 105 patients per arm were evaluable in arms A and B, respectively. The
153 patients' demographics are reported in Table 1.

154 **Comparison between arm A and arm B**

155 As reported in Table 2, there was a significant difference between arms A and B in the overall detection
156 rates of PCa (50.5% vs. 29.5%, $p=0.002$) and csPCa (43.9% vs. 18.1%, $p<0.001$), respectively.

157 **Comparison between targeted and standard biopsy**

158 In arm A, mp-MRI was positive in 81 (75.7%) patients who underwent TB, whilst it was negative in 26
159 (24.3%) patients who underwent SB. A significant difference was recorded when stratifying the patients on
160 the basis of the biopsy approach in terms of the overall detection rates of PCa (60.5% vs. 19.2% vs. 29.5%,
161 $p<0.001$) and csPCa (56.8% vs. 3.8% vs. 18.1%, $p<0.001$) for TB, SB in arm A, and SB in arm B, respectively
162 (Table 2).

163 **Targeted biopsy detection rate according to PIRADS score**

164 In arm A, mp-MRI found one suspected lesion in 54 patients (66.7%) and two suspected lesions in 27
165 patients (33.3%). The rates of detection of PCa and csPCa by TB according to PIRADS scores are reported in
166 Table 3.

167 **Number of samples and pathologic characteristics**

168 In arm A, 800 cores were obtained: 488 by the TB approach and 312 by the SB approach. In arm B, 1260
169 cores were sampled.

170 The median total numbers of biopsies per patient were 6 (5-12) and 12 (12-12) in arms A and B,
171 respectively ($p<0.001$). The median numbers of positive cores per patient were 4 (2-6) and 3 (2-4) in arms A
172 and B, respectively ($p=0.105$).

173 In the subgroup analysis, the median numbers of positive cores per patient were 4 (3-6), 1 (1-1) and 3 (2-4)
174 by TB in both arms, SB in arm A and SB in arm B, respectively ($p=0.001$).

175 Pathological characteristics are reported in Table 4.

176

177 **DISCUSSION**

178 The advent of mp-MRI has changed the approach to prostate biopsy, allowing clinicians to direct biopsies to
179 suspected lesions rather than operating randomly. In 2009, it was estimated that the cost of unnecessary
180 prostate biopsies was greater than that of mp-MRI[20].

181 Biopsy-naïve men seem to be the ideal population for mp-MRI: this imaging method has, in fact, great
182 potential to reduce over-diagnosis in men with high risk of indolent disease detection with random biopsy.

183 The simplest MRI-targeted biopsy strategy is the cognitive approach, which directs visually targeted
184 samples to the suspicious ROI highlighted on mp-MRI. Three RCTs have compared a first biopsy pathway
185 based on mp-MRI to 12-core SB alone, producing conflicting results[8,21,22]. The first two studies
186 concluded that the PCa detection rate was higher in the mp-MRI group[21,22]. However, in the most recent
187 RCT, the authors reported that the mp-MRI group had comparable detection rates of PCa and csPCa,
188 compared to the control group[8].

189 MRI/TRUS fusion software-based targeted biopsy represents the most accurate and practical targeted
190 biopsy strategy[23]. One RCT that used fusion biopsy in a diagnostic pathway based on mp-MRI was
191 published[9]. In the mp-MRI group, two-core fusion biopsy of mp-MRI-suspected lesions and 12-core SB
192 were performed. No significant differences were detected in either the PCa (59.0% vs. 54.0%) or csPCa
193 detection rate (44.0% vs. 49.0%) between the mp-MRI and control groups (12-core SB), respectively. In
194 contrast, some non-randomized studies comparing MRI-targeted biopsy and SB in biopsy-naïve men have
195 concluded that the approach using mp-MRI and subsequent fusion biopsy limited over-detection of
196 clinically insignificant PCa while providing greater detection of csPCa than SB alone[24-28].

197 To the best of our knowledge, this study was the first RCT comparing PCa detection rates between a
198 diagnostic pathway, based on mp-MRI and subsequent MRI/TRUS fusion software-guided targeted biopsy
199 alone, with the standard pathway, based on SB, in a cohort of biopsy-naïve men.

200 The first report of our RCT seemed to confirm the potential role of mp-MRI as a first-line technique in the
201 diagnostic pathway of biopsy-naïve patients with suspected PCa, according to our inclusion criteria.

202 PCa was diagnosed in 50.5% of patients in the mp-MRI group, with 87.0% of cases being clinically
203 significant. These data significantly outperformed the results of the standard pathway. In this group, the
204 overall detection of PCa was 29.5%, similar to the results of previously published series of SB in biopsy-
205 naïve patients[29]. We emphasize that the present study was restricted to patients with PSA **levels up to 15**
206 ng/ml and negative DRE only.

207 The differences in PCa detection rates between the arms of the study were greater than those found in
208 earlier RCTs[8,9], perhaps due to the different protocols used (cognitive biopsy[8], two-core fusion
209 biopsy[9]) and the patient selection criteria.

210 When stratifying the population in terms of the approach to biopsy, we found that TB in sub-arm A MRI+
211 had the best results in terms of the overall detection rate of PCa (60.5%) and the rate of csPCa detected
212 (93.9%). We emphasize that the analysis in the different subgroups might have been affected by the
213 underpowered sample size.

214 The usefulness of the PIRADS classification was emphasized by our findings: a significantly higher detection
215 rate in terms of overall detection of PCa and csPCa in PIRADS 4 and 5 lesions, compared to PIRADS 3

216 lesions, was found. The results in Table 4 suggested that PIRADS 3 lesions might not receive biopsy,
217 although all of them were diagnosed as csPCa after biopsy.

218 The pathological results confirmed the superiority of the mp-MRI pathway in terms of the quality of biopsy
219 samples. Fewer biopsy samples per patient were necessary in arm A, compared to arm B. The median total
220 and maximum CCL and maximum CCI were significantly higher in arm A, compared to arm B.

221 Our results seemed to contribute to confirming the role of mp-MRI in avoiding unnecessary biopsies. In
222 sub-arm A MRI-, only one csPCa (3.8%) was diagnosed. This finding could suggest that prostate biopsy in a
223 biopsy-naïve man with suspicion of PCa but negative mp-MRI could be avoided in the near future.
224 Nevertheless, strict follow-up of these patients is recommended until more robust data are available.

225 The main strength of the current study was its prospective RCT design, in accordance with Good Clinical
226 Practice Guidelines. The results were reported according to the START recommendations. Moreover, the
227 accuracy in terms of histopathological evaluation was guaranteed by the involvement of a single expert
228 uropathologist. mp-MRI was performed according to standardized protocols and was reported using the
229 PIRADS system. This RCT was based on the creation of a new diagnostic pathway, which was possible owing
230 to collaboration among the experts of three radiology centres and a urology division qualified in innovative
231 PCa diagnosis and treatment.

232 A limitation of this approach could be the lack of reproducibility in other centres (i.e., lack of skilled staff or
233 technologies). Moreover, we well know that the reproducibility of a single-centre RCT is not comparable to
234 multicentre-study results. It is possible that the adoption of PIRADS, version 2.0[30], or the use of a 3-T MRI
235 would have resulted in even better diagnostic performance of mp-MRI, although a recent systematic
236 review did not support this hypothesis[6]. Further limitations included the lack of correlation with specimen
237 pathology and the heterogeneity of the mp-MRI equipment. Finally, as previously stated, some
238 comparisons between the subgroups might have been less reliable due to the small sample size.

239

240 **CONCLUSIONS**

241 In the setting of biopsy-naïve men with suspected PCa, PSA **levels up to** 15 ng/ml and negative DRE, pre-
242 biopsy mp-MRI allowed us to detect greater numbers of PCa and csPCa, compared to 12-core SB.
243 Moreover, biopsy samples resulted in more information in terms of CCL and CCI. Our results supported that
244 mp-MRI could be considered prior to a first prostate biopsy. Larger sample sizes would definitely confirm
245 our data.

246

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328 **FIGURE LEGEND**

329 Fig.1 – Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study. mp-MRI =
330 multiparametric magnetic resonance imaging; PSA = prostate-specific antigen.

Table 1 – Demographic characteristics of the study population. mp-MRI = multiparametric magnetic resonance imaging; PSA = prostate-specific antigen. Data for continuous variables are reported as the median (IQR).

	Arm A (mp-MRI group)		Arm B (control group)
Group size, n	107		105
Age, yr	64 (58-70)		66 (60-70)
PSA, ng/ml	5.9 (4.8-7.5)		6.7 (5.5-8.5)
Prostate volume, ml	46.2 (34.5-71.6)		45.7 (34.6-65.0)
	TB	SB (Arm A)	SB (Arm B)
Group size, n	81	26	105
Age, yr	64 (59-70)	63 (58-69)	66 (60-70)
PSA, ng/ml	5.9 (4.8-7.3)	6.1 (5.3-7.5)	6.7 (5.5-8.5)
Prostate volume, ml	44.4 (34.2-67.3)	55.6 (39.5-72.6)	45.7 (34.6-65.0)

Table 2 – Comparison of cancer detection rates in terms of randomization arm and biopsy approach. mp-MRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; csPCa = clinically significant

	Arm A (mp-MRI group)		Arm B (control group)	p-value
Group size, n	107		105	
Overall detection of PCa, n (%)	54 (50.5)		31 (29.5)	0.002
Overall detection of csPCa, n (%)	47 (43.9)		19 (18.1)	<0.001
Ratio of overall detection of csPCa/PCa, %	87.0		61.3	0.013
	TB	SB (Arm A)	SB (Arm B)	p-value
Group size, n	81	26	105	
Overall detection of PCa, n (%)	49 (60.5)	5 (19.2)	31 (29.5)	<0.001
Overall detection of csPCa, n (%)	46 (56.8)	1 (3.8)	19 (18.1)	<0.001
Ratio of overall detection of csPCa/PCa, %	93.9	20.0	61.3	<0.001

prostate cancer; TB = targeted biopsy; SB = standard biopsy.

Table 3 – Comparison of cancer detection rates in sub-arm A MRI+ in terms of PIRADS score. PIRADS = Prostate Imaging Reporting and Data System; PCa = prostate cancer; csPCa = clinically significant prostate cancer.

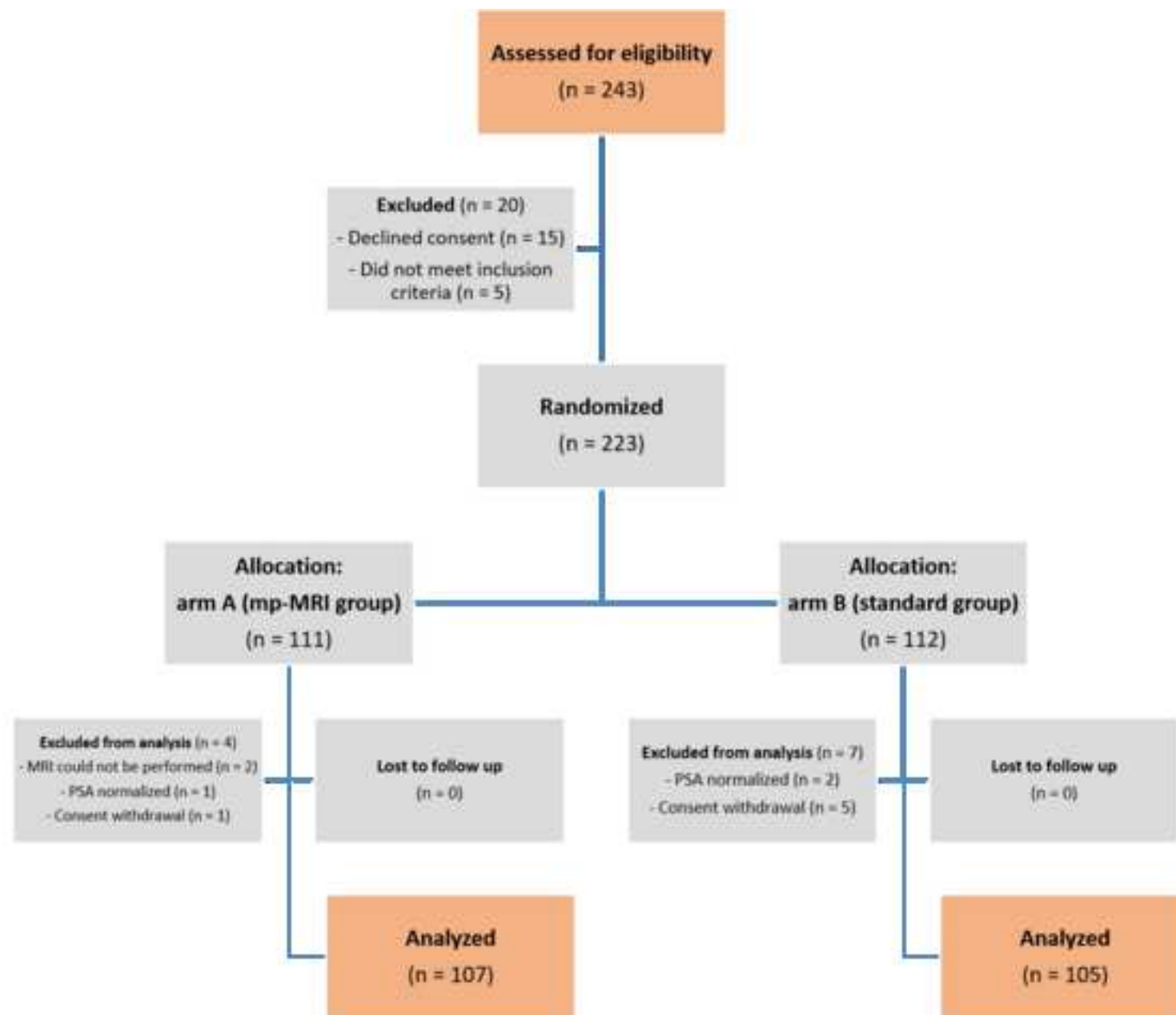
	PIRADS score 3	PIRADS score 4	PIRADS score 5	p-value
Group size, n (%)	24	40	16	
Overall detection of PCa, n (%)	3 (12.5)	32 (80.0)	14 (87.5)	<0.001
Overall detection of csPCa, n (%)	3 (12.5)	30 (75)	13 (81.3)	<0.001
Ratio of overall detection of csPCa/PCa, %	100.0	93.8	92.9	1.000

Table 4 – Histopathological characteristics of the study population. mp-MRI = multiparametric magnetic resonance imaging; GS = Gleason score; SB = standard biopsy; TB = targeted biopsy; CCL = cancer core length; CCI = cancer core invasion. Data for continuous variables are presented as the median (IQR).

	Arm A (mp-MRI group)	Arm B (control group)	p-value	
Group size, n	107	105		
PCa, n (%)	54 (50.5)	31 (29.5)	0.002	
Biopsy GS, n (%)				
• 6	10 (18.5)	17 (54.8)	0.002	
• 7	38 (70.4)	11 (35.5)		
• 8	5 (9.3)	2 (6.5)		
• >8	1 (1.9)	1 (3.2)		
Total CCL, mm	16 (8-31)	5 (2-20)	0.005	
Maximum CCL, mm	7 (5-9)	4 (2-8)	0.013	
Maximum CCI, %	60 (33-77)	25 (14-67)	0.010	
	TB	SB (Arm A)	SB (Arm B)	p-value
Group size, n	81	26	105	
PCa, n (%)	49 (60.5)	5 (19.2)	31 (29.5)	<0.001
Biopsy GS, n (%)				
• 6	5 (10.2)	5 (100)	17 (54.8)	<0.001
• 7	38 (77.6)	0 (0)	11 (35.5)	
• 8	5 (10.2)	0 (0)	2 (6.5)	
• >8	1 (2.0)	0 (0)	1 (3.2)	
Total CCL, mm	18 (10-32)	3 (2-3)	5 (2-20)	0.048
Maximum CCL, mm	8 (6-10)	2 (1-3)	4 (2-8)	0.064
Maximum CCI, %	67 (33-80)	10 (9-25)	25 (14-67)	0.062

Illustration

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*Take Home Message

This randomized trial included 212 biopsy-naïve patients with suspected prostate cancer (PCa), randomized to pre-biopsy multiparametric-MRI (mp-MRI), or standard biopsy. The detection rate of PCa and clinically significant PCa in mp-MRI group was higher if compared to standard group.