Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study

*Olivier Rouvière, Philippe Puech, Raphaële Renard-Penna, Michel Claudon, Catherine Roy, Florence Mège-Lechevallier, Myriam Decaussin-Petrucci, Marine Dubreuil-Chambardel, Laurent Magaud, Laurent Remontet, Alain Ruffion, Marc Colombel, Sébastien Crouzet, Anne-Marie Schott, Laurent Lemaitre, Muriel Rabilloud, Nicolas Grenier, for the MRI-FIRST Investigators**

Summary

Background Whether multiparametric MRI improves the detection of clinically significant prostate cancer and avoids the need for systematic biopsy in biopsy-naive patients remains controversial. We aimed to investigate whether using this approach before biopsy would improve detection of clinically significant prostate cancer in biopsy-naive patients.

Methods In this prospective, multicentre, paired diagnostic study, done at 16 centres in France, we enrolled patients aged 18–75 years with prostate-specific antigen concentrations of 20 ng/mL or less, and with stage T2c or lower prostate cancer. Eligible patients had been referred for prostate multiparametric MRI before a first set of prostate biopsies, with a planned interval of less than 3 months between MRI and biopsies. An operator masked to multiparametric MRI results did a systematic biopsy by obtaining 12 systematic cores and up to two cores targeting hypoechoic lesions. In the same patient, another operator targeted up to two lesions seen on MRI with a Likert score of 3 or higher (three cores per lesion) using targeted biopsy based on multiparametric MRI findings. Patients with negative multiparametric MRI (Likert score ≤2) had systematic biopsy only. The primary outcome was the detection of clinically significant prostate cancer of International Society of Urological Pathology grade group 2 or higher (csPCa-A), analysed in all patients who received both systematic and targeted biopsies and whose results from both were available for pathological central review, including patients who had protocol deviations. This study is registered with ClinicalTrials.gov, number NCT02485379, and is closed to new participants.

Findings Between July 15, 2015, and Aug 11, 2016, we enrolled 275 patients. 24 (9%) were excluded from the analysis. 53 (21%) of 251 analysed patients had negative (Likert ≤2) multiparametric MRI. csPCa-A was detected in 94 (37%) of 251 patients. 13 (14%) of these 94 patients were diagnosed by systematic biopsy only, 19 (20%) by targeted biopsy only, and 62 (66%) by both techniques. Detection of csPCa-A by systematic biopsy (29·9%, 95% CI 24·3–36·0) and targeted biopsy (32·3%, 26·5–38·4) did not differ significantly (p=0·38). csPCa-A would have been missed in 5·2% (95% CI 2·8–8·7) of patients had systematic biopsy not been done, and in 7·6% (4·6–11·6) of patients had targeted biopsy not been done. Four grade 3 post-biopsy adverse events were reported (3 cases of prostatitis, and 1 case of urinary retention with haematuria).

Interpretation There was no difference between systematic biopsy and targeted biopsy in the detection of ISUP grade group 2 or higher prostate cancer; however, this detection was improved by combining both techniques and both techniques showed substantial added value. Thus, obtaining a multiparametric MRI before biopsy in biopsy-naive patients can improve the detection of clinically significant prostate cancer but does not seem to avoid the need for systematic biopsy.

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Introduction

Multiparametric MRI has excellent sensitivity for detecting prostate cancer classified as grade group 2 or higher, according to the International Society of Urological Pathology (ISUP),[1,2] and is increasingly used to locate suspicious lesions before biopsy.[3] Most guidelines recommend pre-biopsy multiparametric MRI in patients with a history of negative biopsy and persistent suspicion of prostate cancer.[4,6] However, whether pre-biopsy multiparametric MRI should be performed in biopsy-naive patients remains unclear.[3,7–9]

Two aspects should be considered when assessing the role of multiparametric MRI in biopsy-naive patients. The first is the improvement in detection of clinically significant prostate cancer—ie, the added value of biopsies targeting lesions identified by MRI, compared with the classical diagnostic pathway that uses systematic biopsy. The second is the added value of systematic biopsy in prostate areas that appear normal on multiparametric MRI.

Results from two prospective multicentre studies have clarified these matters. In the PRECISION study,[10] 500 biopsy-naive patients were randomly assigned to

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*All MRI-FIRST investigators are listed in the appendix

Service d'Imagerie Urinaire et Vasculaire (Prof O Rouvière MD, M Dubreuil-Chambardel PhD), **Service d'Anatomo-Pathologie** (F Mège-Lechevallier MD), **and Service d'Urologie** (Prof M Colombel MD, Prof S Crouzet MD), **Hôpital Edouard Herriot, Service d'Urologie** (Prof A Ruffion MD), **Service d'Anatomo-Pathologie** (M Decaussin-Petrucci MD), **Center Hospitalier Lyon Sud, Pôle de Santé Publique** (L Magaud PhD, Prof A-M Schott MD), **and Service de Biostatistique et Bioinformatique** (L Remontet MD, M Rabilloud MD), **Hospices Civils de Lyon, Lyon, France; Faculté de Médecine Lyon Est** (Prof O Rouvière, Prof M Colombel, Prof S Crouzet) **and Faculté de Médecine Lyon Sud** (M Decaussin-Petrucci) **Université Lyon 1, Université de Lyon** (L Remontet, M Rabilloud), **Lyon, France; Service de Radiologie, CHU Lille, INSERM, Université de Lille, Lille, France** (Prof P Puech MD, Prof L Lemaitre MD); **U1189 - ONCO-THAI - Image Assisted Laser Therapy for Oncology, Lille, France** (Prof P Puech, Prof L Lemaitre); **Services de Radiologie, Hôpitaux Tenon et Pitié Salpétrière, AP-HP, GRC-UPMC n°5 Oncotype-URO, Sorbonne Universités, Paris, France** (Prof R Renard-Penna MD); **IADI, INSERM, Université de Lorraine, Nancy, France**

(Prof M Claudon MD); **Service de Radiologie, CHRU Nancy, Nancy, France** (Prof M Claudon); **CHU de Strasbourg, Nouvel Hôpital Civil, Strasbourg, France** (Prof C Roy MD); **Health Services and Performance Research, EA 7425 HESPER, Université de Lyon, Lyon, France** (L Magaud, Prof A-M Schott); **CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, Villeurbanne, France** (L Remontet, M Rabilloud); **Centre de Recherche en Cancérologie de Lyon - INSERM 1052 CNRS 5286, Centre Léon Bérard, Université Lyon 1, Lyon, France** (Prof A Ruffion); **and Service d'Imagerie Diagnostique et Interventionnelle de l'Adulte, CHU de Bordeaux, Université de Bordeaux, France** (Prof N Grenier MD)

Correspondence to:
Prof Olivier Rouvière, Service d'Imagerie Urinaire et Vasculaire, Pavillon B, Hôpital Edouard Herriot, 69437 Lyon cedex 03, France
olivier.rouviere@netcourrier.com

See Online for appendix

Research in context

Evidence before this study

We searched PubMed for publications in English or French using the search terms "prostate cancer", "MRI", "prostate biopsy", "systematic biopsy", and "targeted biopsy". When MRI-FIRST was designed in 2013, no prospective randomised trials had compared systematic and targeted biopsy in biopsy-naive patients. At least three systematic reviews, published in 2014 and 2015, suggested that targeted biopsy detected more clinically significant prostate cancer than did systematic biopsy. However, one of these reviews showed that the improvement in detection of clinically significant prostate cancer because of targeted biopsy was substantial in patients with a history of negative biopsy, but was only marginal in biopsy-naive men. At least five prospective single-centre randomised trials, published between 2015 and 2017, gave contradictory results regarding whether targeted biopsy could improve detection of clinically significant prostate cancer in biopsy-naive patients. The prospective multicentre PROMIS study, published in 2017, assessed multiparametric MRI and systematic biopsy against template prostate mapping biopsy in biopsy-naive men and showed that multiparametric MRI was significantly more sensitive than systematic biopsy in detecting clinically significant prostate cancer, defined as International Society of Urocological pathology (ISUP) grade group 3 or higher tumours, or tumours with maximum cancer core length of at least 6 mm. The prospective multicentre PRECISION study, published in 2018, randomly assigned biopsy-naive men to either systematic biopsy without multiparametric MRI or to pre-biopsy multiparametric MRI with no biopsy if the multiparametric MRI was negative, and only to targeted biopsy if the multiparametric MRI was positive. The detection rate of ISUP grade group 2 or higher tumours was significantly higher in men assigned to multiparametric MRI and targeted biopsy than in those assigned to systematic biopsy. By contrast, the detection of clinically insignificant tumours (ISUP grade group 1 tumours) was significantly higher in patients assigned to systematic biopsy.

Added value of this study

Rather than randomly assigning patients to either systematic or targeted biopsy, we chose to do both biopsy techniques in the same biopsy-naive men. This approach allowed us to separately investigate the added value of systematic and targeted biopsy by analysing discordant pairs. The results of this study nuance the results of the PRECISION trial. Indeed, we found that both systematic and targeted biopsy had substantial added value in detecting ISUP grade group 2 or higher tumours since a third of these were detected by only one biopsy technique. The added value of systematic biopsy was marginal only for the detection of ISUP grade group 3 or higher tumours. Similar to the PRECISION trial, targeted biopsy in MRI-FIRST detected significantly fewer low-volume, low-grade tumours than did systematic biopsy.

Implications of all the available evidence

Findings from both the MRI-FIRST and PRECISION trials suggest that multiparametric MRI could be safely used as a triage test for the detection of ISUP grade group 3 or higher cancers, and that targeted biopsy has added value in the detection of ISUP grade group 2 or higher cancers. The use of targeted biopsy alone could decrease the detection of non-significant prostate cancer, but the added value of systematic biopsy could still be substantial for the detection of ISUP grade group 2 or higher cancers, which might be optimised when both approaches are combined. Further research is needed to assess the influence of the number of targeted cores on targeted biopsy accuracy, which was lower (on average) in MRI-FIRST than in the PRECISION trial.

either systematic biopsy without multiparametric MRI, or to multiparametric MRI with targeted biopsy only (in the case of positive multiparametric MRI) or no biopsy (in the case of negative multiparametric MRI). The detection of ISUP grade group 2 or higher cancers was significantly higher in men assigned to multiparametric MRI and targeted biopsy (38%) than in those assigned to systematic biopsy (26%; adjusted difference 12 percentage points, 95% CI 4–20, p=0·005). However, this study did not investigate whether combining systematic biopsy and targeted biopsy could increase detection of clinically significant prostate cancer. The PROMIS study[11] assessed multiparametric MRI and systematic biopsy against template prostate mapping biopsy in 576 biopsy-naive men. The negative predictive value of multiparametric MRI was 89% (95% CI 83–94) for clinically significant prostate cancer, defined as ISUP grade group 3 or higher cancers or those with a maximum cancer core length (MCCL) of 6 mm or longer. However, the negative predictive value was 76% (69–82) for ISUP grade group 2 or higher cancers.[11] This suggests that targeted biopsy alone might not provide optimal detection of ISUP grade group 2 or higher cancers, and that systematic biopsy might still detect some clinically significant prostate cancers that are missed by targeted biopsy.

We present the results of the MRI-FIRST trial, a prospective multicentre study in biopsy-naive patients that compared, in the same patients, the detection of ISUP grade group 2 or higher cancers, obtained by 12–14 core systematic biopsy and 3–6 core targeted biopsy.

Methods

Study design and participants

The study was done in 16 centres in France (11 university hospitals, two cancer centres, and three private hospitals) that were experienced in prostate multiparametric MRI and biopsy (appendix p 3). Participants were recruited in outpatient clinics by local urologists, among patients referred for suspicion of prostate cancer on the basis of increased prostate-specific antigen concentration,

abnormal digital rectal examination, or family history of prostate cancer. Eligible men had no history of prostate biopsy, were aged between 18 and 75 years, had a prostate-specific antigen concentration of 20 ng/mL or less, had a digital rectal examination that did not suggest extracapsular (T3) disease (ie, all patients had prostate cancer stage ≤T2c), were suitable candidates for biopsy of the prostate and for multiparametric MRI, and had no history of hip prosthesis, androgen deprivation therapy, pelvic radiotherapy, or prostate cancer diagnosed after transurethral resection of the prostate. The MRI-FIRST protocol was approved by an ethics committee (Comité de Protection des Personnes Sud-Est IV, decision A-15-170) and all included patients provided written informed consent. The full protocol of this trial is included in the appendix (pp 16–99).

Procedures

All patients first had prostate multiparametric MRI. Centres could use their routine imaging protocol, if it was compliant with international guidelines.[12] Multiparametric MRI was done at 1·5T or 3T, with an external coil, with or without an endorectal coil. The imaging protocol included T2-weighted imaging obtained in at least two orthogonal planes (or three-dimensional T2-weighted imaging), axial diffusion-weighted imaging obtained with multiple b-values, and axial contrast-enhanced dynamic imaging obtained after intravenous injection of a bolus of gadolinium chelates at a dose of 0·1 mmol/kg of bodyweight (appendix pp 4, 5).

Multiparametric MRI interpretation was done at the local site by a single radiologist who had access to clinical details. There was no centralised reading before biopsy and local radiologists did not have centralised training. However, the quality of multiparametric MRI was checked at the start of the study. We assessed the likelihood of clinically significant prostate cancer using 5-level Likert scoring (1, highly unlikely; 2, unlikely; 3, equivocal; 4, likely; 5, highly likely). Because a score of 1 corresponded with normal prostate areas, focal lesions received a score of at least 2.

Transrectal ultrasound-guided prostate biopsy was done within 3 months of multiparametric MRI, by two independent senior operators (urologists or radiologists) with experience in prostate biopsy (appendix p 3), under local anaesthesia. A first operator, masked to multiparametric MRI findings, did a systematic biopsy. Two cores (one medial, one lateral) were first obtained in each prostate sextant with visual guidance. Up to two additional cores targeting a hypoechoic lesion could also be obtained if needed. Then, another operator with knowledge of multiparametric MRI findings did a targeted biopsy by targeting up to two lesions with a Likert score of 3 or higher, with three cores taken from each lesion. If there were more than two lesions on MRI with a Likert score of 3 or higher, the two lesions with the highest Likert scores (or the largest ones if the scores were equal) were targeted. Patients with negative multiparametric MRI (Likert score ≤2) had systematic biopsy only.

Radiologists also provided the Prostate Imaging—Reporting and Data System version 2 (PI-RADSv2)[12] score of each lesion, in addition to the Likert score. However, in case of discordance, the Likert score was used for biopsy decision.

For targeted biopsy, centres used the guiding method corresponding to the standard of care at their institution. Five centres used cognitive guidance, ten centres used MRI–ultrasound fusion (n=7 Urostation, Koelis, La Tronche, France; n=2 Smart Fusion, Applio 500, Toshiba, Tochigi, Japan; n=1 Percunav, Epiq, Philips, Best, Netherlands).[13] One centre used cognitive guidance with the help of contrast-enhanced ultrasound after intravenous injection of ultrasound contrast medium (Sonovue, Bracco, Milan, Italy) when needed.[14]

Adverse events occurring between patient inclusion and until 1 week after prostate biopsy were reported by local investigators and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.3.

All biopsies were centrally reviewed by a uropathologist (FM-L) with 12 years of experience; systematic biopsy and targeted biopsy were reviewed separately and in random order. In each case, we assessed the MCCL and highest ISUP grade group.[15] When the grade group differed to that reported by the local pathologist, biopsy findings were reviewed by a third uropathologist (MD-P) who had 13 years of experience. The final grade group was then decided by consensus. We used the results of centralised reading in the rest of the study. Patients who withdrew their consent were excluded from the analysis, as were those for whom centralised reading findings for systematic biopsy and targeted biopsy were not available (ie, patients who did not have multiparametric MRI or prostate biopsy, patients for whom biopsy slides were not received for centralised reading, or patients for whom systematic and targeted cores were not clearly labelled for central reading).

Outcomes

We used three clinically significant prostate cancer (csPCa) definitions, based on the 2014 ISUP classification:[15] grade group 2 or higher tumours (csPCa-A); grade group 1 tumours with MCCL of 6 mm or longer or grade group 2 or higher tumours (csPCa-B), and grade group 3 or higher tumours (csPCa-C). The primary outcome was the detection of csPCa-A. The secondary outcomes were the detection of csPCa-B and of csPCa-C, and the detection of non-clinically significant prostate cancer (ISUP grade group 1 cancers with MCCL <6 mm).

Statistical analysis

We assumed the total prevalence of csPCa-A detected by at least one of the two biopsy strategies to be 25%.[16] We

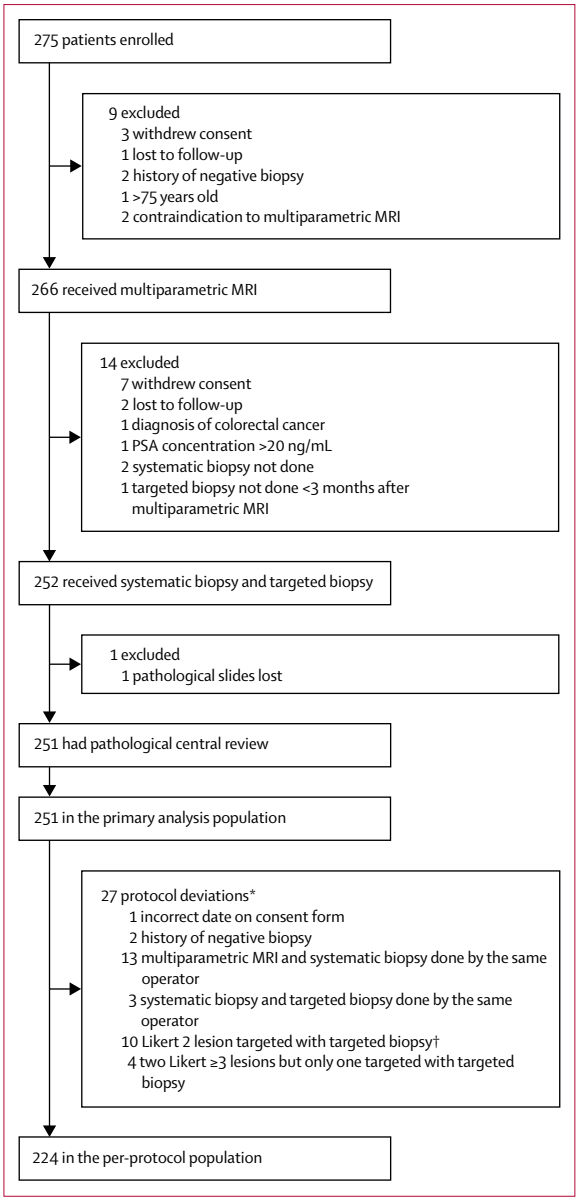

Figure: **Trial profile**
PSA=prostate-specific antigen. *Some patients had more than one major deviation (total number of 33 major deviations in 27 patients). †Eight of these ten patients had only lesions with a Likert score of 2. Two patients had two lesions (one with a Likert score of 2 and one with a score of 3).

also assumed that 30% of csPCa-A would be detected by targeted biopsy only, and 6% by systematic biopsy only.[17] Thus, the expected probability of detecting csPCa-A by targeted biopsy only was 7·5% and by systematic biopsy only was 1·5% (9% of discordant pairs). According to these parameters, the sample size needed to conclude a significant difference with a bilateral alpha risk of 5%, power of 90%, and using a McNemar test for paired data, was 225 patients. To account for protocol deviations, we anticipated the inclusion of 275 patients. We calculated the sample size using nQuery software (version 5.0).

	Patients (n=251)
Median age, years	64 (59–68)
Median prostate-specific antigen concentration	6·5 ng/mL (5·6–9·6)
Median prostate volume	50 cc (38–63)
Digital rectal examination	
T1c	172 (69%)
T2a	54 (22%)
T2b	17 (7%)
T2c	6 (2%)
Missing data	2 (1%)
Likert score	
1 (no lesion)	36 (14%)
2	17 (7%)
3	60 (24%)
4	72 (29%)
5	66 (26%)

Data are median (IQR) or n (%).

Table 1: **Patient characteristics**

We did the primary analysis in all patients for whom the results of systematic biopsy and targeted biopsy were available for central reading, including patients with protocol deviations; we also analysed the per-protocol population after excluding patients with protocol deviations. We presented outcomes according to the standards of reporting for targeted biopsy studies guidelines.[18] We described characteristics using medians and IQRs for quantitative characteristics, and absolute and relative frequencies for qualitative characteristics. We estimated the proportion of patients with csPCa-A detected by targeted biopsy and systematic biopsy and obtained their 95% CIs using the Clopper-Pearson exact method, and compared the proportions using the McNemar test with continuity correction. We present the added value of targeted biopsy and systematic biopsy—ie, the proportion of patients with csPCa-A detected by targeted biopsy only and by systematic biopsy only—with their 95% CI. We did the same analyses for secondary outcomes.

We also compared proportions of patients with csPCa-A in subgroups stratified according to clinical stage (T1c *vs* T2a–2c), prostate-specific antigen concentration (<10 ng/mL *vs* ≥10 ng/mL), prostate volume (≤50 mL *vs* >50 mL), and by type of targeted biopsy guidance (cognitive guidance vs MRI–ultrasound fusion guidance). For these subgroup comparisons, we used the exact McNemar test when the expected number of discordant pairs was too small. We did all analyses using R (version 3.3.2).

This study is registered with ClinicalTrials.gov, number NCT02485379.

Role of the funding source

The funder of the study had no role in study design, data collection, data interpretation, or writing of the report.

	No targeted biopsies (negative multiparametric MRI)*	Targeted biopsies†							Total
		Benign tissue	ISUP grade group 1, MCCL <3 mm	ISUP grade group 1, MCCL ≥3 mm and <6 mm	ISUP grade group 1, MCCL ≥6 mm	ISUP grade group 2	ISUP grade group 3	ISUP grade group ≥4	
Benign tissue	32	76	4	0	2	3	2	1	120
ISUP grade group 1, MCCL <3 mm	6	13	3	1	1	4	1	0	29
ISUP grade group 1, MCCL ≥3 and <6 mm	2	6	2	1	4	5	0	0	20
ISUP grade group 1, MCCL ≥6 mm	0	2	2	0	0	2	1	0	7
ISUP grade group 2	4	4	1	0	2	16	8	2	37
ISUP grade group 3	0	1	0	0	0	0	13	0	14
ISUP grade group ≥4	1	0	0	0	0	1	4	18	24
Total	45	102	12	2	9	31	29	21	251

Data are numbers of patients. ISUP=International Society of Urological Pathology. MCCL=maximum cancer core length. *Patients with negative multiparametric MRI (Likert ≤2) only had systematic biopsies. †Of patients who had targeted biopsies, eight patients had Likert 2 lesions only.

Table 2: **Results of systematic and targeted biopsies**

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 15, 2015, and Aug 11, 2016, 275 men were enrolled. After the exclusion of 24 (9%) patients from the analysis (figure), central reading results for systematic biopsy and targeted biopsy were available for 251 patients (table 1), including 27 patients with protocol deviations (figure).

36 (14%) patients had no lesions on multiparametric MRI (table 1). In the remaining 215 patients, 321 lesions were described; the Likert and PI-RADSv2 scores would have yielded a concordant biopsy decision in 293 (91%) lesions (appendix p 6).

In 41 patients, one (n=20) or two (n=21) additional cores were obtained in hypoechoic lesions. The total number of systematic biopsy cores was 3070 (mean 12·2 cores per patient).

Ten patients had lesions with a Likert score of 2 targeted at biopsy, contrary to protocol. Eight of these ten patients had only lesions with a Likert score of 2. Thus, 45 (85%) of 53 patients with negative (Likert score ≤2) multiparametric MRI underwent systematic biopsy without targeted biopsy. In the remaining 206 patients who had targeted biopsy, 286 lesions were targeted. The total number of targeted biopsy cores was 810 (mean 3·2 cores per patient).

csPCa-A was detected in 94 (37%) of 251 patients. Of these 94 cases, 13 (14%) were detected by systematic biopsy only, 19 (20%) by targeted biopsy only, and 62 (66%) by both techniques (table 2). The proportions of csPCa-A detected by systematic biopsy (29·9%, 95% CI 24·3–36·0) and targeted biopsy (32·3%, 26·5–38·4) did not differ significantly (p=0·38; table 3). csPCa-A would have been missed in 5·2% (95% CI 2·8–8·7) of patients if systematic biopsy had not been done, and in 7·6% (4·6–11·6) of patients if targeted biopsy had not been done (table 3). There was discordance between local and centralised biopsy reading for the presence of csPCa-A in 15 (6%) of the 251 patients for systematic biopsy and 8 (4%) of the 206 patients for targeted biopsy (appendix pp 7–8).

csPCa-B was detected in 105 (42%) of 251 patients (15 by systematic biopsy only, 23 by targeted biopsy only, and 67 by both techniques) and csPCa-C was detected in 53 (21%) of 251 patients (3 by systematic biopsy only, 15 by targeted biopsy only, and 35 by both techniques; table 2). csPCa-B detection by systematic biopsy and targeted biopsy were not different (p=0·26; table 3); csPCa-C detection by systematic biopsy was significantly lower than by targeted biopsy (p=0·0095; table 3). Non-clinically significant prostate cancer was detected in

	ISUP grade group ≥2 (csPCa-A)	ISUP grade group ≥2 or ISUP grade group 1 with MCCL ≥6 mm (csPCa-B)	ISUP grade group ≥3 (csPCa-C)
Systematic biopsy	29·9% (24·3–36·0)	32·7% (26·9–38·9)	15·1% (10·9–20·2)
Targeted biopsy	32·3% (26·5–38·4)	35·9% (29·9–42·1)	19·9% (15·2–25·4)
Systematic biopsy and targeted biopsy	37·5% (31·4–43·8)	41·8% (35·7–48·2)	21·1% (16·2–26·7)
Added value of systematic biopsy*	5·2% (2·8–8·7)	6·0% (3·4–9·7)	1·2% (0·2–3·5)
Added value of targeted biopsy†	7·6% (4·6–11·6)	9·2% (5·9–13·4)	6·0% (3·4–9·7)
p value‡	0·38	0·26	0·0095

Results are % (95% CI) of 251 patients, or p value. ISUP=International Society of Urological Pathology. csPCa=clinically significant prostate cancer. MCCL=maximal cancer core length. *Difference between the detection rate obtained by combined systematic biopsy and targeted biopsy, and by targeted biopsy alone. †Difference between the detection rate obtained by combined systematic biopsy and targeted biopsy, and by systematic biopsy alone. ‡From the comparison of detection rates obtained by systematic biopsy and targeted biopsy.

Table 3: **Detection of clinically significant prostate cancer, according to biopsy strategy**

56 (22%) of 251 patients (42 by systematic biopsy only, 7 by targeted biopsy only, and 7 by both techniques). The detection of non-clinically significant prostate cancer was significantly higher for systematic biopsy (19·5%, 95% CI 14·8–25·0) than for targeted biopsy (5·6%, 3·1–9·2; p<0·0001).

Systematic biopsy detected csPCa-A in five (11%) of the 45 patients with negative multiparametric MRI who did not have targeted biopsy. Systematic biopsy also detected csPCa-A missed by targeted biopsy in eight (4%) of the 206 patients having a targeted biopsy (table 2). Of those eight patients, five had a lesion with a Likert score of 3 or higher in the sextant that showed the most pejorative findings at systematic biopsy, two in an adjacent ipsilateral sextant, and one in a non-adjacent ipsilateral sextant; targeted biopsy guidance method was cognitive guidance in four patients, MRI–ultrasound fusion in three patients, and contrast-enhanced ultrasound guidance in one patient.

Detection of csPCa-A by targeted biopsy and systematic biopsy did not differ in any of the analysed subgroups (table 4). Additional biopsies targeting hypoechoic lesions detected csPCa-A that was missed by systematic cores in one patient (appendix p 9).

Results of targeted and systematic biopsy according to the patients' Likert score are presented in table 5. Targeted biopsy identified csPCa-A in 12 (12%) of the 99 lesions with a Likert score of 3, in 30 (29%) of the 103 lesions with a Likert score of 4, and in 54 (74%) of the 73 lesions with a Likert score of 5 (appendix p 10). Targeted biopsy also identified csPCa-A in 53 (27%) of the 194 lesions smaller than or equal to 15 mm and in 44 (48%) of the 92 lesions larger than 15 mm (appendix p 11). Biopsy results obtained in each centre are shown in the appendix (pp 12, 13). Four grade 3 adverse events occurred within the week after prostate biopsy (prostatitis, n=3; urinary retention with haematuria, n=1).

The per-protocol analysis yielded similar results (appendix pp 14, 15). csPCa-A was detected in 90 (40%) of 224 patients (13 by systematic biopsy only, 19 by targeted biopsy only, and 58 by both techniques), csPCa-B in 99 (44%) patients (15 systematic biopsy only, 21 targeted biopsy only, 63 both), csPCa-C in 49 (22%) patients (2 systematic biopsy only, 15 targeted biopsy only, 32 both), and non-clinically significant prostate cancer in 51 (23%) patients (38 systematic biopsy only, 6 targeted biopsy only, 7 both). The proportion of prostate cancers detected by systematic biopsy and targeted biopsy were not different, either for csPCa-A (31·7%, 95% CI 25·7–38·2 for systematic biopsy *vs* 34·4%, 28·2–41·0 for targeted biopsy; p=0·38) or for csPCa-B (34·8%, 28·6–41·5 *vs* 37·5%, 31·1–44·2; p=0·40). Systematic biopsy detected csPCa-C in significantly fewer patients than targeted biopsy (15·2%, 95% CI 10·7–20·6 *vs* 21%, 15·8–26·9; p=0·0036) and non-clinically significant prostate cancer in significantly more patients than targeted biopsy (20%, 15–26 *vs* 5·8%, 3·1–9·7; p<0·0001).

	n*	Systematic biopsy	Targeted biopsy	p value†
T1c stage	172	22·7% (16·6–29·7)	25·6% (19·2–32·8)	0·40
T2a–2c stage	77	46·8% (35·5–58·5)	48·1% (36·5–59·7)	1
PSA <10 ng/mL	195	26·2% (20·1–32·9)	28·7% (22·5–35·6)	0·42
PSA ≥10 ng/mL	56	42·9% (29·7–56·8)	44·6% (31·3–58·5)	1
Prostate volume ≤50 mL	121	40·5% (31·7–49·8)	42·1% (33·2–51·5)	0·82
Prostate volume >50 mL	114	16·7% (10·3–24·8)	21·1% (14–29·7)	0·18
Centres using cognitive guidance	109	32·1% (23·5–41·7)	33·9% (25·1–43·6)	0·79
Centres using MRI-ultrasound fusion guidance	134	27·6% (20·2–36·0)	30·6% (22·9–39·1)	0·45

Data are % (95% CI), unless otherwise specified. csPCa-A=clinically significant prostate cancer, defined as tumours with an International Society of Urological Pathology grade group 2 or higher. PSA=prostate-specific antigen. *Missing data for two patients for clinical stage, and for 16 patients for prostate volume; eight patients in whom targeted biopsies were done under contrast-enhanced ultrasound guidance were excluded from the cognitive guidance versus MRI–ultrasound fusion guidance subgroup analysis. †From the comparison of detection rates obtained by systematic biopsy and targeted biopsy in each subgroup.

Table 4: **Detection rates of csPCa-A, by subgroup**

Discussion

In MRI-FIRST, detection of csPCa-A did not differ between targeted biopsy and systematic biopsy. Detection of csPCa-B also did not differ between the two biopsy

	Patients (N)	Systematic biopsy				Targeted biopsy				Combined			
		ns PCa	csPCa-A	csPCa-B	csPCa-C	ns PCa	csPCa-A	csPCa-B	csPCa-C	ns PCa	csPCa-A	csPCa-B	csPCa-C
1	36	7 (19%)	3 (8%)	3 (8%)	1 (3%)	..	..	..	..	7 (19%)	3 (8%)	3 (8%)	1 (3%)
2*	17	2 (12%)	3 (18%)	3 (18%)	1 (6%)	0 (0%)	1 (6%)	1 (6%)	0 (0%)	2 (12%)	3 (18%)	3 (18%)	1 (6%)
3	60	10 (17%)	9 (15%)	10 (17%)	2 (3%)	3 (5%)	7 (12%)	8 (13%)	3 (5%)	12 (20%)	10 (17%)	12 (20%)	3 (5%)
4	72	21 (29%)	15 (21%)	20 (28%)	5 (7%)	11 (15%)	22 (31%)	23 (32%)	12 (17%)	26 (36%)	23 (32%)	27 (38%)	12 (17%)
5	66	9 (14%)	45 (68%)	46 (70%)	29 (44%)	0 (0%)	51 (77%)	58 (88%)	35 (53%)	9 (14%)	55 (83%)	60 (91%)	36 (55%)
Total	251	49	75	82	38	14	81	90	50	56	94	105	53

Data are n or n (%). ns PCa=non-significant prostate cancer, defined as International Society of Urological Pathology (ISUP) grade group 1 tumours with a maximum cancer core length (MCCL) <6 mm. csPCa-A=clinically significant prostate cancer with ISUP grade group 2 or higher tumours. csPCa-B=clinically significant prostate cancer with ISUP grade group 1 tumours with MCCL 6 mm or longer, or with ISUP grade group 2 or higher tumours. csPCa-C=clinically significant prostate cancer with ISUP grade group 3 or higher tumours. *Eight patients with a maximum Likert score of 2 had targeted biopsy, contrary to the protocol.

Table 5: **Results of targeted and systematic biopsy, by maximum Likert score**

methods. For detection of csPCa-A and csPCa-B, detection improved when both systematic and targeted biopsy were combined. Detection of csPCa-C was significantly lower with systematic biopsy than with targeted biopsy, and targeted biopsy detected significantly fewer non-clinically significant prostate cancer tumours than did systematic biopsy.

Several important methodological choices were made in the design of this study. We assessed systematic biopsy and targeted biopsy in the same patients, which guarantees the comparability of groups and allows separate assessment of the added value of targeted biopsy and systematic biopsy by analysing discordant pairs. Furthermore, each centre was free to use its own routine multiparametric MRI protocol (provided it was compliant with international guidelines)[12] and the guiding method used for targeted biopsy. This approach induced heterogeneity in the data, but better reflects routine practice. There was a centralised review of pathological slides to try and reduce the interobserver variability of the reference test. We did not use the PI-RADSv2 score to trigger targeted biopsy because this score was launched at the beginning of 2015, and was not fully assessed at the start of this study; we therefore preferred to use the Likert score, which, despite being subjective, is strongly predictive of biopsy findings.[11,16,19] The two scores showed highly concordant findings in our study, and thus using the PI-RADSv2 score would have had little effect on biopsy decision. It remains unclear whether a positivity cutoff Likert score of 3 or 4 should be used to trigger targeted biopsy;[20] we chose a cutoff of 3 rather than 4 to improve the sensitivity of targeted biopsy and assess the nature of lesions with a Likert score of 3.

Because there is no consensus on the matter,[20,21] we used three definitions for clinically significant prostate cancer. This approach allows assessment of the added value of systematic biopsy and targeted biopsy across a panel of tumour aggressiveness, which was based mainly on ISUP grade groups. The use of MCCL in clinically significant prostate cancer definitions is debatable, since a given MCCL derived from systematic biopsy cores corresponds, on average, with a larger tumour volume than that derived from targeted biopsy cores. This approach was therefore used only for secondary objectives, with the view to separate large and small low-grade tumours.

The finding that targeted biopsy did not diagnose csPCa-A tumours in a significantly greater proportion of patients than systematic biopsy does not mean that pre-biopsy multiparametric MRI is not useful to improve detection of grade group 2 or higher tumours. Indeed, a third of these tumours were detected by use of only one biopsy technique; csPCa-A would have been missed in 7·6% of the patients had targeted biopsy not been done, and in 5·2% had systematic biopsy not been done. This finding suggests that detection of such tumours is improved when systematic biopsy and targeted biopsy are combined. We noted similar findings for the wider definition of clinically significant prostate cancer, which also included ISUP grade group 1 with MCCL of 6 mm or more (csPCa-B), but for the most aggressive forms (ISUP grade group ≥3 [csPCa-C]), the added value of systematic biopsy was marginal. Thus, using multiparametric MRI as a triage test (no biopsy when multiparametric MRI is negative, targeted biopsy only when multiparametric MRI is positive) might be a valid approach, but only for diagnosing highly aggressive tumours. The per-protocol analysis, which excluded patients with protocol deviations, showed similar results to those in our primary analysis population.

The subgroup analysis did not identify any factor with a substantial effect on the difference in detection between targeted biopsy and systematic biopsy. In particular, there was no clear difference between the results of centres using cognitive guidance and those using MRI–ultrasound fusion guidance. A meta-analysis[22] also did not find a significant difference between cognitive guidance and MRI–ultrasound fusion guidance.[22] Among the eight patients with positive multiparametric MRI in whom systematic biopsy detected ISUP grade group 2 or higher tumours missed by targeted biopsy, five had a suspicious lesion on MRI in the sextant in which systematic biopsy found grade group 2 or higher tumour. This finding suggests that, at least for these five patients, targeted biopsy might have missed (or undersampled) the target. The precision of guiding methods under routine conditions of use has been seldom investigated[23] and is probably still suboptimal considering the size of targeted lesions. Herein, only three targeted cores per lesion were obtained; increasing the number of cores taken per target could have partially compensated the guiding imprecision and improved targeted biopsy results.[17] The proportion of csPCa-A detected by targeted biopsy was substantially greater in lesions larger than 15 mm (48%) than in lesions smaller than or equal to 15 mm (27%). This difference could be due to high-grade cancers being larger than benign lesions or low-grade cancers, as suggested by comparisons with prostatectomy specimens.[24] It could also be partly explained by small high-grade cancers being more likely to be missed by targeted biopsy.

One centre used contrast-enhanced ultrasound for targeted biopsy guidance. Although promising results with this method have been found,[14] it is still investigational and can be difficult to reproduce. The decision to allow this guidance method in the protocol was part of our pragmatic approach that aimed to investigate routine practice, thus avoiding selection bias by letting the centres use the targeting technique they were used to. If the protocol had forbidden contrast-enhanced ultrasound guidance, the centre using this method in routine practice might have been inclined to include only patients who were likely to have large lesions (eg, patients with positive digital rectal examination), and exclude other patients to be able to use contrast-enhanced ultrasound. We believe such selection bias, which is difficult to detect,

can cause large discrepancies between results obtained in trials and in real life. However, only eight patients had contrast-enhanced ultrasound guidance and this is very unlikely to have changed the results.

We observed a difference of 2·4 percentage points between the detection of ISUP grade group 2 or higher tumours obtained by systematic biopsy and targeted biopsy, which is notably smaller than that reported in the PRECISION study.[10] Both trials included experienced academic and non-academic centres and used a pragmatic approach by allowing centres to use their routine multiparametric MRI protocols and targeting methods. Furthermore, in both trials, the number of patients was calculated to achieve a statistical power of 90%. The populations included were also similar in terms of age (median age 64 years in MRI-FIRST *vs* 64·4–64·5 years in PRECISION), prostate-specific antigen concentration (6·5 ng/mL *vs* 6·5–6·75 ng/mL), and prostate volume (50 cc *vs* 43·7–46·0 cc). However, the proportion of patients with abnormal digital rectal examination was higher in the MRI-FIRST population (31% *vs* 14–15%), which might explain the lower proportion of patients with negative multiparametric MRI (21% *vs* 29%), and the higher proportion of patients with highly suspicious lesions (Likert or PI-RADSv2 score of 5, 26% *vs* 21%) than in PRECISION. In MRI-FIRST, the mean number of cores taken per patient was higher for systematic biopsy (12·2 *vs* 11·2) and lower for targeted biopsy (3·2 *vs* 3·8) than in PRECISION. It is unlikely that the greater number of systematic cores per patient explains the higher detection by systematic biopsy, since additional samples obtained in hypoechoic lesions detected additional ISUP grade group 2 or higher tumours in only one patient. However, the lower number of targeted cores per patient could explain the fact that the detection rate obtained by targeted biopsy was lower in MRI-FIRST. Indeed, the biopsy of a maximum of two suspicious lesions per patient with a maximum of three targeted cores per lesion was allowed, compared with a maximum of three suspicious lesions with up to four targeted cores per lesion in PRECISION. Given the imprecision of targeting methods discussed above, this approach could have been of importance. Further studies are necessary to assess the optimal number of targeted cores as a function of the lesion size and prostate volume.

Although the addition of systematic biopsy to targeted biopsy improved the detection of clinically significant prostate cancer in MRI-FIRST, it also significantly increased the detection of patients with low-volume and low-grade tumours, which could induce over-treatment. This finding is in accordance with the results of PRECISION.[10]

Taken together, these results and those of the PRECISION trial strongly suggest that targeted biopsy has added value in biopsy-naive patients and improves the detection of clinically significant prostate cancer. However, the results of MRI-FIRST do nuance the results of the PRECISION trial. First, the added value of targeted biopsy seems to depend on the definition of clinically significant prostate cancer, which needs to be standardised. Second, the added value of systematic biopsy might still be substantial in patients having targeted biopsy, at least for the diagnosis of ISUP group grade 2 or higher cancers, and therefore the conditions remain to be defined under which systematic biopsy could be safely avoided in patients who had a pre-biopsy multiparametric MRI. Finally, the minimal number of targeted cores ensuring accuracy for targeted biopsy needs to be defined. It should be noted that, for the three definitions of clinically significant prostate cancer used, the added values of systematic biopsy (1·2–6·0%) and targeted biopsy (6·0–9·2%) were moderate compared with the detection obtained when both approaches are combined (21·1–41·8%), and it should also be noted that the effect of improved clinically significant prostate cancer detection on patient survival is yet to be investigated.

MRI-FIRST does have limitations. First, clinically significant prostate cancer might have been missed by both targeted biopsy and systematic biopsy in some patients. We did not use template prostate mapping biopsy as a reference standard because it needs spinal or general anaesthesia, which could have discouraged some patients and induced a selection bias. Furthermore, we were interested in assessing whether pre-biopsy multiparametric MRI could improve detection of clinically significant prostate cancer, compared with the current standard of care, which is transrectal ultrasound-guided systematic biopsy, not template prostate mapping biopsy. Second, the performance of targeted biopsy might have been reduced by systematic biopsy-induced bleeding artefacts and gland swelling. However, these artefacts are usually mild. Third, all the study centres had experience in prostate multiparametric MRI and biopsy, and two centres enrolled more than a third of the overall patient population, which limits the generalisability of the results. Assessing the interobserver agreement in multiparametric MRI interpretation was beyond the scope of this study. Nonetheless, an ancillary study is planned to investigate the cross-reading of the multiparametric MRI of 100 study patients by radiologists of varying experience. Fourth, we have no follow-up data for patients. Fifth, we did not use risk calculators, which can help select patients for biopsy,[25] and their effect on the results cannot be assessed. Similarly, whether clinical parameters or biomarkers (such as prostate-specific antigen density) can predict the patients who might benefit from targeted biopsy (or systematic biopsy)[26–30] remains outside the scope of this study but is an important subject for future research. Finally, cost-effectiveness and feasibility of obtaining pre-biopsy multiparametric MRI in all patients referred for biopsy were beyond the scope of this study.

In conclusion, there was no significant difference between the detection rate of ISUP grade group 2 or higher tumours obtained by systematic biopsy and

targeted biopsy, but analysis of discordant pairs suggests that tumour detection was improved when systematic biopsy and targeted biopsy were combined, and thus the addition of multiparametric MRI information does improve detection of clinically significant prostate cancer. Analysis of secondary outcome data suggests that systematic biopsy could be omitted only for the detection of ISUP grade group 3 or higher tumours.

Contributors

OR, PP, RR-P, NG, LL, MCl, CR, LM, AR, MCo, SC, A-MS, and MR designed the study. MD-C and LM collected and assembled the data. FM-L and MD-P did the pathological central review. LR and MR did the statistical analysis. OR, PP, RR-P, NG, MCl, CR, LM, LR, MD-C, A-MS, and MR interpreted and analysed the data. LM and A-MS provided the figure. OR did the literature search and wrote the first draft. All authors were involved in the critical review of the manuscript and approved the final version. All authors agreed to be accountable for all aspects of the work.

Declaration of interests

OR reports payment of travel expenses by Philips Medical System, outside the submitted work. NG is a member of the Supersonic Imagine Advisory Board and reports personal fees from Guerbet group outside the submitted work. All other authors declare no competing interests.

Data sharing

Individual participant data will be available (including data dictionaries). Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figure, and appendices), will be shared. The study protocol, statistical analysis plan, and analytical code will also be available. Data will be available between 9 and 36 months after Article publication. Data may be shared with investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose. Data is available for analyses that achieve the aims of the approved proposal. Requests for data should be directed by email to Prof Olivier Rouvière. To gain access, data requestors will need to sign a data access agreement.

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