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

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Added value of prostate systematic and targeted biopsy based on multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective multicentre paired diagnostic study

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Added value of prostate systematic and targeted biopsy based on multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective multicentre paired diagnostic study

Summary

Background

Whether multiparametric magnetic resonance imaging (mpMRI) improves the detection of clinically-significant prostate cancer and avoids systematic biopsy (SBx) in biopsy-naïve patients remains controversial.

Methods

In this prospective multicentre paired diagnostic study, we compared clinically-significant prostate cancer detection rates obtained by SBx and targeted biopsy (TBx) in the same biopsy-naïve patients. We included 275 patients (≤75 years, PSA ≤20 ng/ml, stage ≤T2c) in 16 centres. An operator blinded to mpMRI results performed SBx by obtaining 12 systematic cores and up to two cores targeting hypoechoic lesions. Another operator performed TBx by targeting up to two Likert ≥3 lesions (3 cores/lesion). The primary outcome was the percentage of patients with International Society of Urological Pathology (ISUP) grade group ≥2 cancer. The primary analysis was performed on the overall population (all patients with SBx and TBx results, including patients with protocol deviations). The study (ClinicalTrials.gov NCT02485379) is closed to new participants.

Findings

Twenty-four patients were excluded. Fifty-three (21·1%) of 251 analysed patients had negative (Likert ≤2) mpMRI. ISUP grade group ≥2 cancer was detected in 94 (37·5%) of the 251 patients. Thirteen (13·8%) of these 94 patients were diagnosed by SBx only, 19 (20·2%) by TBx only, and 62 (66%) by both techniques. Detection rates obtained by SBx (29·9%, 95% confidence interval [95CI]: 24·3-36·0) and TBx (32·3%, 95CI: 26·5-38·4) were not significantly different (P=0·38). ISUP grade group ≥2 cancer would have been missed in 5·2% (95CI: 2·8-8·7) of patients had SBx not been performed, and

in 7·6% (95CI: 4·6-11·6) of patients had TBx not been performed. Four grade-3 post-biopsy adverse events were reported (prostatitis, n=3; urinary retention with haematuria, n=1).

Interpretation

SBx and TBx both showed substantial added value, and the detection of ISUP grade group ≥2 cancer was improved by combining these techniques.

Funding

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Introduction

Multiparametric magnetic resonance imaging (mpMRI) has excellent sensitivity for detecting prostate cancer (PCa) classified as grade group ≥2 according to the International Society of Urological Pathology (ISUP),[1,2] and is increasingly used to localise suspicious lesions before biopsy.[3] Most current guidelines recommend pre-biopsy mpMRI in patients with history of negative biopsy and persistent suspicion of PCa.[4,6] However, it remains unclear whether pre-biopsy mpMRI should be performed in biopsy-naïve patients.[3,7-9]

Two aspects should be considered when evaluating the role of mpMRI in biopsy-naïve patients. The first is the improvement in the detection of clinically-significant prostate cancer (csPCa), i.e. the added value of biopsies targeting magnetic resonance (MR) lesions (TBx) compared to the classical diagnostic pathway using systematic biopsy (SBx). The second is the added value of SBx in prostate areas that appear normal on mpMRI.

Two prospective multicentre studies recently shed light on these matters. In the PRECISION study, 500 biopsy-naïve patients were randomized to either SBx without mpMRI or to mpMRI with TBx only in case of positive mpMRI and no biopsy in case of negative mpMRI. The detection rate of ISUP grade group ≥2 cancers was significantly higher in men assigned to mpMRI and TBx (38%) than in those assigned to SBx (26%; P=0.005). However, this study did not evaluate whether combining SBx and TBx could provide higher csPCa detection rates.[10] The PROMIS study evaluated mpMRI and SBx against template prostate mapping (TPM) biopsy in 576 biopsy-naïve men. The negative predictive value of mpMRI was 89% (95% confidence interval [95CI]: 83-94) for csPCa defined as ISUP grade group ≥3 or maximum cancer core length (MCCL) ≥6 mm. However, it was only 76% (95CI: 69-82) for ISUP grade group ≥2 cancers.[11] This suggests that TBx alone might not provide optimal detection of ISUP grade group ≥2 cancers and that SBx might still detect some csPCa missed by TBx.

We present herein the results of the MRI-FIRST trial, a prospective multicentre study in biopsy-naïve patients that compared in the same patients the detection rates of ISUP grade group ≥2 cancers obtained by 12-14 core SBx and 3-6 core TBx.

Material and Methods

Study design and participants

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).

The study was conducted in 16 centres in France (11 university hospitals, two cancer centres, and three private hospitals) experienced in prostate mpMRI and biopsy (appendix p 3). Participants were recruited in outpatient clinics by local urologists among patients referred for suspicion of PCa based on elevated prostate specific antigen (PSA), abnormal digital rectal examination, and/or family history of prostate cancer. Eligible men had no history of prostate biopsy, were between 18 and 75 years of age, had a PSA level of 20 ng/mL or less, had a digital rectal examination that did not suggest extracapsular (T3) disease, were suitable candidates for biopsy of the prostate and for mpMRI, and had no history of hip prosthesis, pelvic radiation or PCa diagnosed on transurethral resection of the prostate.

Procedures

All patients first underwent prostate mpMRI. Centres could use their routine imaging protocol provided it was compliant with international guidelines.[12] mpMRI was performed 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 3D 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 body weight (appendix pp4-5).

mpMRI interpretation was performed 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 undergo centralised training. However, the quality of mpMRI was checked at the start of the study. The

likelihood of csPCa was assessed using 5-level Likert scoring (1: highly unlikely; 2: unlikely; 3: equivocal; 4: likely; 5: highly likely). Because a score of 1 corresponded to normal prostate areas, focal lesions received a score ≥2.

Transrectal ultrasound-guided (TRUS) prostate biopsy was performed within three months of mpMRI, by two independent senior operators (urologists or radiologists) with experience in prostate biopsy (appendix p 3), under local anaesthesia. A first operator, blinded to mpMRI findings, performed SBx. Two cores (one medial, one lateral) were first obtained in each prostate sextant using visual guidance. Up to two additional cores targeting a hypoechoic lesion could also be obtained if needed. Then, another operator with knowledge of mpMRI findings performed TBx by targeting up to two Likert ≥3 lesions, with three cores taken from each lesion. If there were more than two Likert ≥3 lesions, the two lesions with the highest Likert scores (or the largest ones if the scores were equal) were targeted. Patients with negative mpMRI (Likert ≤2) underwent SBx 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 TBx, centres used the guiding method corresponding to the standard of care at their institution. Five centres used cognitive guidance, 10 centres used magnetic resonance/ultrasound (MR/US) fusion (Urostation, Koelis, La Tronche, France, n=7; Smart Fusion, Applio 500, Toshiba, Tochigi, Japan, n=2; Percunav, Epiq, Philips, Best, The Netherlands, n=1).[13] One centre used cognitive guidance with help of contrast-enhanced ultrasound (CEUS) after intravenous injection of ultrasound contrast medium (Sonovue, Bracco, Milan, Italy) when needed.[14]

Adverse events occurring between patient inclusion and until one 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 underwent centralised review by an uro-pathologist (FML) with 12 years of experience; SBx and TBx were reviewed separately and in random order. In each case, the MCCL and highest ISUP grade group were assessed.[15] When the grade group was different from that reported by the local pathologist, biopsy findings were reviewed by a third uro-pathologist (MDP) who had 13

years of experience. The final grade group was then decided by consensus. The results of centralised reading were used 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 SBx and TBx were not available (i.e. patients who did not undergo mpMRI 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

Three csPCa definitions based on the 2014 ISUP classification[15] were used: grade group ≥2 tumours (csPCa-A), grade group 1 tumours with MCCL ≥6 mm or grade group ≥2 tumours (csPCa-B), and grade group ≥3 tumours (csPCa-C). The primary outcome criterion was the detection of csPCa-A. The secondary outcome criteria were the detection of csPCa-B and of csPCa-C, and the detection of non-significant PCa (ISUP grade group 1 cancers with MCCL <6 mm).

Statistical analysis

The total prevalence of csPCa-A detected by at least one of the two biopsy strategies was assumed to be 25%.[16] We also assumed that 30% of csPCa-A would be detected by TBx only, and 6% by SBx only.[17] Thus, expected probabilities to detect csPCa-A by TBx only and SBx only were 7·5% and 1·5% respectively (9% of discordant pairs). According to these parameters, the sample size needed to conclude to 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. The sample size was computed using nQuery software, version 5.0.

The primary analysis was performed on the overall population (i.e. all patients for whom the results of SBx and TBx were available for central reading, including patients with protocol deviations); analysis of the per-protocol population (i.e. after exclusion of protocol deviations) was also performed. Outcomes were presented according to the Standards of reporting for TBx studies (START) guidelines.[18] Characteristics were described using medians and inter-quartile ranges for

quantitative characteristics, and absolute and relative frequencies for qualitative characteristics. Percentages of patients with csPCa-A detected by TBx and SBx were estimated with their 95CI obtained using the Clopper-Pearson exact method and compared using the McNemar test with continuity correction. The added value of TBx and SBx, i.e. the proportion of patients with csPCa-A respectively detected by TBx only and by SBx only, were presented with their 95CI. Similar analyses were performed for secondary outcomes.

Percentages of patients with csPCa-A were also compared in subgroups stratified according to clinical stage, PSA level, prostate volume, and TBx guidance. For these subgroup comparisons, the exact McNemar test was used when the expected number of discordant pairs was too small. All analyses were performed using R software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined by $P<0.05$. The study is registered on ClinicalTrials.gov, identifier NCT02485379.

Role of the funding source

The funder had no role in study design, data collection and analysis, or writing of this paper. The corresponding author had full access to all the data and the final responsibility to submit for publication.

Results

Patient characteristics

From 15 July 2015 to 11 August 2016, 275 men were included. Central reading results of SBx and TBx were available for 251 patients (overall population; Table 1) including 27 patients with protocol deviations (Figure 1).

Thirty-six patients had no lesion on mpMRI (Table 1). In the others, 321 lesions were described; the Likert and PI-RADSv2 scores would have yielded a concordant biopsy decision in 293 (91·3%) 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 SBx cores was 3070 (mean: 12·2 cores per patient).

Eight patients with a Likert score of 2 underwent TBx. Thus, only 45 patients with negative (Likert ≤2) mpMRI underwent SBx without TBx. In the others, 286 lesions were targeted. The total number of TBx cores was 810 (mean: 3·2 cores per patient).

There was discordance between local and centralised biopsy reading for the presence of csPCa-A in 15 (6%) of the 251 patients for SBx and 8 (3·9%) of the 206 patients for TBx (appendix pp 7-8).

Primary outcome

csPCa-A was detected in 94 (37·5%) of the 251 patients. Of these, 13 (13·8%) were detected by SBx only, 19 (20·2%) by TBx only, and 62 (66%) by both techniques (Table 2). csPCa-A detection rates obtained by SBx and TBx were not significantly different (P=0·38). csPCa-A would have been missed in 5·2% (95CI, 2·8-8·7) of patients had SBxnot been performed, and in 7·6% (95CI, 4·6-11·6) of patients had TBx not been performed (Table 3).

Secondary outcomes

csPCa-B was detected in 105 (41·8%) and csPCa-C in 53 (21·1%) of the 251 patients. csPCa-B detection rates obtained by SBx and TBx were not significantly different (P=0·26); csPCa-C detection rates obtained by SBx were significantly lower than those obtained by TBx (P=0·0095; Table 3). Non-significant PCa was detected in 56 patients (22·3%); its detection rate was significantly higher for SBx (19·5%, 95CI: 14·8-25·0) than for TBx (5·6%, 95CI: 3·1-9·2; P<0·0001).

Additional findings

SBx detected csPCa-A in 5 (11·1%) of the 45 patients with negative mpMRI who did not have TBx. SBx also detected csPCa-A missed by TBx in 8 (3·9%) of the 206 patients undergoing TBx (Table 2). Of those 8 patients, 5 had a Likert ≥3 lesion in the sextant that showed the most pejorative findings at SBx, 2 in an adjacent ipsilateral sextant, and 1 in a non-adjacent ipsilateral sextant; TBx

guidance method was cognitive guidance in 4 patients, MR/US fusion in 3 patients and CEUS guidance in 1 patient.

The csPCa-A detection rates obtained by TBx and SBx were not significantly different in any of the analysed sub-groups (Table 4). Additional biopsies targeting hypoechoic lesions detected csPCa-A missed by systematic cores in only one patient (appendix p 9).

Results of targeted and systematic biopsy according to the patients' Likert score are presented in Table 5. TBx found 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). TBx also found csPCa-A in 53 (27%) of the 194 lesions ≤ 15 mm and in 44 (48%) of the 92 lesion >15 mm (appendix p 11). Biopsy results obtained in each centre are detailed in the appendix (p 12-13). Four grade-3 adverse events occurred within the week following prostate biopsy (prostatitis, n=3; urinary retention with haematuria, n=1).

Per-protocol analysis

Analysis in the per-protocol population yielded results similar to those found in the overall population (appendix pp 14-15). Detection rates obtained by SBx and TBx were not significantly different, either for csPCa-A (31·7%, 95CI: 25·7-38·2, versus 34·4%, 95CI: 28·2-41·0; P=0·38) or for csPCa-B (34·8%, 95CI: 28·6-41·5, versus 37·5%, 95CI 31·1-44·2; P=0·40). SBx detected csPCa-C in significantly fewer patients (15·2%, 95CI: 10·7-20·6) than TBx (21%, 95CI: 15·8-26·9; P=0·0036) and non-significant PCa in significantly more patients (20%, 95CI: 15-26) than TBx (5·8%, 95CI: 3·1-9·7; P<0.0001).

Discussion

In the present study, TBx did not significantly outperform SBx for detection of ISUP grade group ≥2 tumours (defined herein as csPCa-A; primary objective) nor grade group 1 tumours with MCCL ≥6 mm or grade group ≥2 tumours (csPCa-B; secondary objective), but in both cases detection rates were improved when SBx and TBx were combined. TBx, however, detected significantly more

grade group ≥3 tumours (csPCa-C secondary objective) and significantly fewer grade group 1 tumours with MCCL <6 mm (non-significant PCa, secondary objective).

Several important methodological choices were made in the design of the present study. SBx and TBx were assessed in the same patients, which guarantees the comparability of groups and allows to separately evaluate the added value of TBx and SBx by analysing discordant pairs. Furthermore, each centre was free to use its routine mpMRI protocol (provided it was compliant with international guidelines)[12] and targeting method. This induced heterogeneity in the data but better reflects routine practice. However, there was a centralised review of pathological slides to reduce as much as possible the interobserver variability of the reference test. We did not use the PI-RADSv2 to trigger TBx because this score was launched at the beginning of 2015 and was not fully evaluated at the start of the present study; we therefore preferred to use the Likert score that, despite being subjective, is strongly predictive of biopsy findings.[11,16,19] The two scores showed highly concordant findings, and using the PI-RADSv2 score would have had little impact on biopsy decision. It remains unclear whether a positivity cut-off score of 3 or 4 should be used to trigger TBx;[20] we chose a cut-off of 3 rather than 4 to improve the sensitivity of TBx 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 csPCa. This allows evaluation of the added value of SBx and TBx across a panel of tumour aggressiveness, which was based mainly on ISUP grade groups. The use of MCCL in csPCa definitions is debatable since a given MCCL derived from SBx cores corresponds, on average, to a larger tumour volume than that derived from TBx cores. This was therefore used only for secondary objectives, with the view to separate large and small low-grade tumours.

The finding that TBx did not diagnose ISUP grade group ≥2 tumours (csPCa-A herein) in a significantly greater proportion of patients than SBx does not mean that pre-biopsy mpMRI is not useful to improve grade group ≥2 tumour detection. Indeed, a third of these were detected by only one biopsy technique; it would have been missed in 7·6% of the patients had TBx not been performed, and in 5·2% had SBx not been performed. This suggests that detection of such tumours is improved when SBx and TBx are combined. A similar situation was found for the wider definition of csPCa that also included ISUP grade group 1 with MCCL ≥6 mm (csPCa-B herein), but for the most aggressive forms

(ISUP grade group ≥3, csPCa-C herein) the added value of SBx was marginal. Thus, using mpMRI as a triage test (no biopsy when mpMRI is negative, TBx only when mpMRI is positive) may be a valid approach, but only for diagnosing highly aggressive tumours. Per-protocol analysis, performed after exclusion of patients with protocol deviations, showed similar results.

Subgroup analysis did not identify any factor with a substantial impact on the difference in detection rates between TBx and SBx. In particular, there was no clear difference between the results of centres using cognitive guidance and those using MR/US fusion guidance. A recent meta-analysis also failed to find significant difference between cognitive guidance and MR/US fusion guidance.[22] Interestingly, among the eight patients with positive mpMRI in whom SBx detected ISUP grade group ≥2 tumours missed by TBx, five had a suspicious MR lesion in the sextant in which SBx found grade group ≥2 tumour. This suggests that, at least for these five patients, TBx may have missed (or undersampled) the target. The precision of guiding methods under routine conditions of use has been seldom evaluated[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 may have partially compensated the guiding imprecision and improved TBx results.[17] The proportion of csPCa-A detected by TBx was substantially greater in lesions >15 mm (48%) than in lesions ≤15 mm (27%). This difference could be due to high-grade cancers being larger than benign lesions or low-grade cancers, as suggested by recent comparisons with prostatectomy specimens.[24] It could also be partly explained by small high-grade cancers being more likely to be missed by TBx.

One centre used CEUS for TBx guidance. Although promising results with this method have been found,[14] it is still investigational and may be difficult to reproduce. The decision to allow this guidance method in the protocol was part of our pragmatic approach that aimed to evaluate routine practice thus avoiding selection bias by letting the centres use the targeting technique they were used to. If the protocol had forbidden CEUS guidance, the centre using this method in routine practice might have been inclined to include only patients who were likely to have large lesions (e.g. patients with positive digital rectal examination), while keeping the others outside the protocol to be free to use CEUS. 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 CEUS guidance and this is very unlikely to have changed the results presented herein.

In the present study we observed a difference of 2·4 percentage points between the ISUP grade group ≥2 tumour detection rates obtained by SBx and TBx, which is markedly inferior to 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 mpMRI 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: 64 versus 64·4-64·5 years), PSA level (6·5 versus 6·5-6·75 ng/mL), and prostate volume (50 versus 43·7-46 cc). However, the proportion of patients with abnormal digital rectal examination was higher in the population of the present study (30·7% versus 14-15%), which may explain the lower proportion of patients with negative mpMRI (21·1% versus 28·9%), and the higher proportion of patients with highly suspicious lesions (Likert/PI-RADSv2 score of 5, 26·2% versus 21·4%). Herein, the mean number of cores taken per patient was greater for SBx (12·2 versus 11·2) and lower for TBx (3·2 versus 3·8). It is unlikely that the greater number of systematic cores per patient explains the higher detection rate obtained by SBx herein, since additional samples obtained in hypoechoic lesions detected additional ISUP grade group ≥2 tumour in only one patient. However, the lower number of targeted cores per patient could explain the fact that the detection rate obtained by TBx was lower in the present study. Indeed, the biopsy of a maximum of two suspicious lesions per patient with a maximum of three targeted cores per lesion was allowed in the present study, compared to 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 may 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 adding SBx to TBx improved the detection of csPCa in the present study, it also significantly increased the detection of patients with low-volume and low-grade tumours, which may induce over-treatment. This is in accordance with the results of PRECISION.[10]

Taken together, the results presented herein and those of the PRECISION trial strongly suggest that TBx have added value in biopsy-naïve patients and improve csPCa detection. However, the results of the present study do nuance the results of the PRECISION trial. First, the added value of TBx seems dependent on the definition of csPCa that needs to be standardized. Second, the added value of SBx may still be substantial in patients undergoing TBx, at least for the diagnosis of ISUP group grade ≥2 cancers, and therefore the conditions under which SBx could be safely avoided in patients who underwent pre-biopsy mpMRI remain to be defined. Third, the minimal number of targeted cores ensuring accuracy for TBx needs to be defined. It also should be noted that, for the three definitions of csPCa used, the added values of SBx (1·2-6·0%) and TBx (6·0-9·2%) were moderate as compared to prevalences (21·1-41·8%) and that the impact on patient survival of improved csPCa detection is yet to be evaluated.

The present study does have limitations. First, csPCa may have been missed by both TBx and SBx in some patients. We did not use TPM biopsy as reference standard because it needs spinal/general anaesthesia, which may have discouraged some patients and induced a selection bias. Furthermore, we were interested in assessing whether pre-biopsy mpMRI could improve csPCa detection as compared to the current standard of care that is transrectal ultrasound-guided SBx and not TPM biopsy. Second, the performance of TBx might have been reduced by SBx-induced bleeding artefacts and gland swelling. However, these artefacts are usually mild. Third, all the study centres had experience in prostate mpMRI and biopsy, and two centres included over a third of the overall population, which limits the generalisability of the results. Assessing the inter-observer agreement in mpMRI interpretation was beyond the scope of this study. Nonetheless, an ancillary study evaluating the cross-reading of the mpMRI of 100 study patients by radiologists of varying experience is planned for the future. Fourth, we have no follow-up data for patients. Fifth, risk-calculators, that may help select patients for biopsy,[25] were not used and their impact on the results cannot be assessed. Similarly, whether clinical parameters and/or biomarkers (such as PSA density) can predict the patients who may benefit from TBx (or SBx)[26-30] remains outside the scope of this study but a subject for future research. Sixth, cost-effectiveness and feasibility of obtaining pre-biopsy mpMRI 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 tumours obtained by SBx and TBx, but analysis of discordant pairs suggests that tumour detection was improved when SBx and TBx were combined, and thus that the addition of mpMRI information does improve csPCa detection. Analysis of secondary outcome data suggests that SBx could be omitted only for the detection of ISUP grade group ≥3 tumours.

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Tables

Table 1: Patient characteristics (overall population)

		N=251
Median age (interquartile range)		64 years (59-68)
Median prostate-specific antigen (interquartile range)		6·5 ng/mL (5·6-9·6)
Median prostate volume (interquartile range)		50 cc (38-63)
Digital rectal examination	T1c	172 (68·5%)
	T2a	54 (21·5%)
	T2b	17 (6·8%)
	T2c	6 (2·4%)
	Missing data	2 (0·8%)
Likert score	1 (no lesion)	36 (14·3%)
	2	17 (6·8%)
	3	60 (23·9%)
	4	72 (28·7%)
	5	66 (26·2%)

Table 2: Results of systematic and targeted biopsy (overall population)

		No TBx (negative mpMRI)[1]	TBx[2]						
			Benign tissue	ISUP GG1, MCCL <3 mm	ISUP GG1, MCCL ∈ [3 mm;6 mm[	ISUP GG1, MCCL ≥6 mm	ISUP GG2	ISUP GG3	ISUP GG≥4	Total
SBx	Benign tissue	32	76	4	0	2	3	2	1	120
	ISUP GG1, MCCL<3 mm	6	13	3	1	1	4	1	0	29
	ISUP GG1, MCCL ∈ [3 mm;6 mm[	2	6	2	1	4	5	0	0	20
	ISUP GG1, MCCL≥6 mm	0	2	2	0	0	2	1	0	7
	ISUP GG2	4	4	1	0	2	16	8	2	37
	ISUP GG3	0	1	0	0	0	0	13	0	14
	ISUP GG≥4	1	0	0	0	0	1	4	18	24
	Total	45	102	12	2	9	31	29	21	251

(1) Patients with negative mpMRI (Likert ≤2) underwent only SBx.

(2) Among patients who underwent TBx, 8 had only Likert 2 lesions.

Patients with International Society of Urological Pathology (ISUP) grade group ≥3 tumours (csPCa-C) are indicated by red cells; patients with ISUP grade group ≥2 tumours (csPCa-A) are indicated by purple and red cells; patients with ISUP grade group 1 tumours with maximum cancer core length (MCCL) ≥6 mm or with ISUP grade group ≥2 tumours (csPCa-B) are indicated by pink, purple, and red cells.

mpMRI: multiparametric magnetic resonance imaging; SBx: systematic biopsies and biopsies targeting a hypoechoic lesion; TBx: biopsies targeting a lesion seen at multiparametric magnetic resonance imaging; ISUP GG: International Society of Urological Pathology grade group.

Table 3: Detection rates of clinically-significant prostate cancer according to the biopsy strategy (overall population)

	ISUP grade group ≥2 (csPCa-A)	P[(1)]	ISUP grade group ≥2 or ISUP grade group 1 with MCCL ≥6 mm (csPCa-B)	P[(1)]	ISUP grade group ≥3 (csPCa-C)	P[(1)]
	Percentage (95% confidence interval)		Percentage (95% confidence interval)		Percentage (95% confidence interval)	
SBx	29·9 (24·3-36·0)	0·38	32·7 (26·9-38·9)	0·26	15·1 (10·9-20·2)	0·0095
TBx	32·3 (26·5-38·4)		35·9 (29·9-42·1)		19·9 (15·2-25·4)	
SBx + TBx	37·5 (31·4-43·8)		41·8 (35·7-48·2)		21·1 (16·2-26·7)	
Added value of SBx[(2)]	5·2 (2·8-8·7)		6·0 (3·4-9·7)		1·2 (0·2-3·5)	
Added value of TBx[(3)]	7·6 (4·6-11·6)		9·2 (5·9-13·4)		6·0 (3·4-9·7)	

(1) P-value comparing the detection rates obtained by SBx and TBx.

(2) Difference between the detection rate obtained by combined SBx + TBx and by TBx alone

(3) Difference between the detection rate obtained by combined SBx + TBx and by SBx alone

csPCa: clinically significant prostate cancer; ISUP: International Society of Urological Pathology; MCCL: maximal cancer core length; SBx: systematic biopsies and biopsies targeting a hypoechoic lesion; TBx: biopsies targeting a lesion seen at multiparametric magnetic resonance imaging.

Table 4: Detection rates of csPCa-A according to clinical stage, PSA level, prostate volume, and guidance method used for targeted biopsy (overall population)

		SBx	TBx	P[(2)]
	Nb Pts[(1)]	Percentage (95% confidence interval)	Percentage (95% confidence interval)	
T1c stage	172	22·7% (16·6-29·7)	25·6% (19·2-32·8)	0·40
T2a-c 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 MR/US fusion guidance	134	27·6% (20·2-36·0)	30·6% (22·9-39·1)	0·45

(1) missing data in 2 patients for clinical stage and in 16 patients for prostate volume; 8 patients in whom targeted biopsies were performed under contrast-enhanced ultrasound guidance were excluded from the cognitive guidance versus MR/US fusion guidance subgroup analysis.

(2) P value comparing the detection rate obtained by SBx and TBx in each subgroup

Nb Pts: Number of patients; SBx: systematic biopsies and biopsies targeting a hypoechoic lesion; TBx: biopsies targeting a lesion seen at multiparametric magnetic resonance imaging; PSA: prostate specific antigen; csPCa-A: clinically significant prostate cancer defined as tumours with an International Society of Urological Pathology grade group ≥2.

Table 5: Results of targeted and systematic biopsy according the maximum Likert score of the patients (overall population)

Maximum Likert score	Patients	SBx				TBx				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[(1)]	17[(1)]	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

(1) 8 patients with a maximum Likert score of 2 had targeted biopsy, contrary to the protocol.

SBx: systematic biopsies and biopsies targeting a hypoechoic lesion; TBx: biopsies targeting a lesion seen at multiparametric magnetic resonance imaging; ns PCa: International Society of Urological Pathology (ISUP) grade group 1 tumours with a maximum cancer core length <6 mm; csPCa-A: ISUP grade group ≥2 tumours; csPCa-B: ISUP grade group 1 tumours with maximum cancer core length (MCCL) ≥6 mm or with ISUP grade group ≥2 tumours; csPCa-C: ISUP grade group ≥3 tumours.

Captions for figures

Figure 1: STARD flow diagram

mpMRI: multiparametric magnetic resonance imaging; SBx: systematic biopsies and biopsies targeting a hypoechoic lesion; TBx: biopsies targeting a lesion seen at multiparametric magnetic resonance imaging; csPCa: clinically-significant prostate cancer; MCCL: maximum cancer core length; ISUP: International Society of Urological Pathology.

(1) Some patients had more than one major deviation (total number of 33 major deviations in 27 patients)

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 the present study was designed (2013), there was no prospective randomized trial comparing systematic and targeted biopsy in biopsy-naïve patients. At least three systematic reviews published in 2014 and 2015 suggested that targeted biopsy detected more clinically-significant prostate cancer (csPCa) than systematic biopsy. However, one of these reviews showed that the improvement in csPCa detection due to targeted biopsy was substantial in patients with history of prior negative biopsy but was only marginal in biopsy-naïve men. At least five prospective single-centre randomized trials published between 2015 and 2017 gave contradictory results as to whether or not targeted biopsy could improve csPCa detection in biopsy-naïve patients. The prospective multicentre PROMIS study, published in 2017, evaluated multiparametric MRI (mpMRI) and systematic biopsy against template prostate mapping biopsy in biopsy-naïve men and showed that mpMRI was significantly more sensitive than systematic biopsy in detecting csPCa defined as International Society of Uropathology (ISUP) grade group ≥3 tumours or tumours with maximum cancer core length ≥6 mm. The prospective multicentre PRECISION study, published in 2018, randomized biopsy-naïve men to either systematic biopsy without mpMRI or to pre-biopsy mpMRI with no biopsy if the mpMRI was negative and only targeted biopsy if the mpMRI was positive. The detection rate of ISUP grade group ≥2 tumours was significantly higher in men assigned to mpMRI and targeted biopsy than in those assigned to systematic biopsy. In contrast, the detection rate 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 randomizing patients to either systematic or targeted biopsy, we chose to perform both biopsy techniques in the same biopsy-naïve men. This allowed to separately evaluate the added value of systematic and targeted biopsy by analysing discordant pairs. The results of the present 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 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 tumours. As in the PRECISION trial, targeted biopsy detected in the present study significantly fewer low-volume low-grade tumours than systematic biopsy.

Implication of all the available evidence

Both MRI-FIRST and PRECISION trials suggest that mpMRI could be safely used as a triage test for the detection of ISUP grade group ≥3 cancers, and that targeted biopsy has added value in the detection of ISUP grade group ≥2 cancers. The use of targeted biopsy alone could decrease the detection of non-significant prostate cancer, but the added value of systematic biopsy may still be substantial for the detection of ISUP grade group ≥2 cancers that may be optimised when both approaches are combined. Further research is needed to evaluate the influence on targeted biopsy accuracy of the number of targeted cores that was lower on average in the present study than in the PRECISION trial.

Author contribution

OR, PP, RRP, NG, LL, MCl, CR, LM, AR, MCo, SC, AMS, and MR designed the study.

MDC and LM collected and assembled the data.

FML and MDP did the pathological central review.

LR and MR did the statistical analysis.

OR, PP, RRP, NG, MCl, CR, LM, LR, MDC, AMS, and MR interpreted and analysed the data.

LM and AMS 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.

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Declaration of interests

Olivier Rouvière reported payment of travel expenses by Philips Medical System, outside the submitted work. Nicolas Grenier is member of the Supersonic Imagine Advisory Board and reported personal fees from Guerbet group outside the submitted work. All other authors declared no competing interest.

Data sharing statement

Will individual participant data be available (including data dictionaries)? Yes

What data in particular will be shared?
Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).

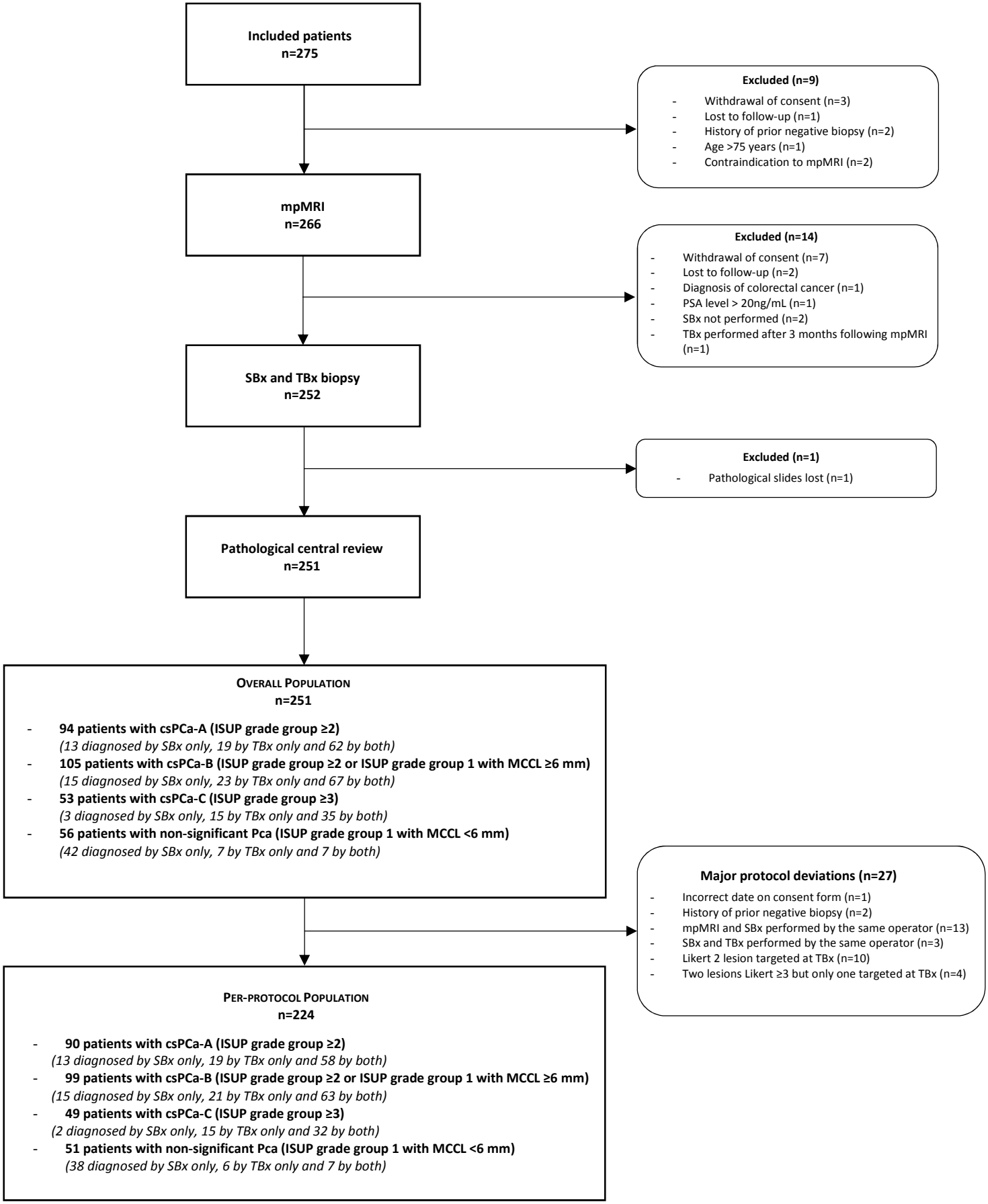
What other documents will be available?
Study Protocol, Statistical Analysis Plan, Analytic Code

When will data be available (start and end dates)?
Beginning 9 months and ending 36 months following article publication.

With whom?
Investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose.

For what types of analyses?
To achieve aims in the approved proposal.

By what mechanism will data be made available?
Proposals should be directed to olivier.rouviere@netcourrier.com. To gain access, data requestors will need to sign a data access agreement.


Included patients
n=275
Excluded (n=9)
- Withdrawal of consent (n=3)
- Lost to follow-up (n=1)
- History of prior negative biopsy (n=2)
- Age >75 years (n=1)
- Contraindication to mpMRI (n=2)
mpMRI
n=266
Excluded (n=14)
- Withdrawal of consent (n=7)
- Lost to follow-up (n=2)
- Diagnosis of colorectal cancer (n=1)
- PSA level > 20ng/mL (n=1)
- SBx not performed (n=2)
- TBx performed after 3 months following mpMRI (n=1)
SBx and TBx biopsy
n=252
Excluded (n=1)
- Pathological slides lost (n=1)
Pathological central review
n=251
OVERALL POPULATION
n=251
- 94 patients with csPCa-A (ISUP grade group ≥2)
(13 diagnosed by SBx only, 19 by TBx only and 62 by both)
- 105 patients with csPCa-B (ISUP grade group ≥2 or ISUP grade group 1 with MCCL ≥6 mm)
(15 diagnosed by SBx only, 23 by TBx only and 67 by both)
- 53 patients with csPCa-C (ISUP grade group ≥3)
(3 diagnosed by SBx only, 15 by TBx only and 35 by both)
- 56 patients with non-significant Pca (ISUP grade group 1 with MCCL <6 mm)
(42 diagnosed by SBx only, 7 by TBx only and 7 by both)
Major protocol deviations (n=27)
- Incorrect date on consent form (n=1)
- History of prior negative biopsy (n=2)
- mpMRI and SBx performed by the same operator (n=13)
- SBx and TBx performed by the same operator (n=3)
- Likert 2 lesion targeted at TBx (n=10)
- Two lesions Likert ≥3 but only one targeted at TBx (n=4)
PER-PROTOCOL POPULATION
n=224
- 90 patients with csPCa-A (ISUP grade group ≥2)
(13 diagnosed by SBx only, 19 by TBx only and 58 by both)
- 99 patients with csPCa-B (ISUP grade group ≥2 or ISUP grade group 1 with MCCL ≥6 mm)
(15 diagnosed by SBx only, 21 by TBx only and 63 by both)
- 49 patients with csPCa-C (ISUP grade group ≥3)
(2 diagnosed by SBx only, 15 by TBx only and 32 by both)
- 51 patients with non-significant Pca (ISUP grade group 1 with MCCL <6 mm)
(38 diagnosed by SBx only, 6 by TBx only and 7 by both)