Review Article

Value of systematic sampling in an mp-MRI targeted prostate biopsy strategy

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Abstract: The clinical utility of systematic prostate biopsy in addition to multi-parametric magnetic resonance imagining (mp-MRI) targeted biopsy pathways remains unclear. Despite radiological advancements in mp-MRI and utilisation of international standardised reporting systems (i.e., PI-RADS, LIKERT), undetected clinically significant prostate cancer (csPCa) on imaging persists. This has prevented the widespread adoption of an exclusively targeted biopsy approach. The current evidence on csPCa cancer detection rates in mp-MRI targeted alone and combined with a non-targeted systematic sampling is presented. Arguments for and against routine limited systematic sampling as an adjunct to an mp-MRI targeted biopsy are discussed. Our review will report the clinical utility of a combined sampling strategy on csPCa detection rate. The available evidence suggests that we are yet to reach a stage where non-targeted systematic prostate biopsy can be routinely omitted in mp-MRI targeted prostate biopsy pathways. Research should focus on improving the accuracy of mp-MRI, prostate biopsy techniques, and in identifying those men that will most benefit from a combined prostate biopsy. Such strategies may help future urologists reduce the burden of non-targeted cores in modern mp-MRI prostate biopsy pathways.

Keywords: Prostate cancer; prostate neoplasm; biopsy; magnetic resonance imagining (MRI); grading

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Introduction

Conventional transrectal ultrasound guided (TRUS) biopsy for prostate cancer, without a prior multi-parametric magnetic resonance imagining (mp-MRI), has been associated with the underdetection of clinically significant prostate cancer (csPCa) (1,2). The PROMIS trial demonstrated the limited accuracy of standard TRUS biopsy, and validated the benefits of pre-biopsy mp-MRI (1). This has resulted in a recent shift in diagnostic pathway design to incorporate pre-biopsy mp-MRI followed by a targeted biopsy approach as standard of care (3,4).

The case for mp-MRI targeted prostate biopsy was further strengthened by the results of the PRECISION randomised controlled study, in which targeted biopsy alone performed superiorly in the detection of csPCa compared to conventional systematic biopsy (2). In that trial, however, non-targeted systematic biopsies were not performed

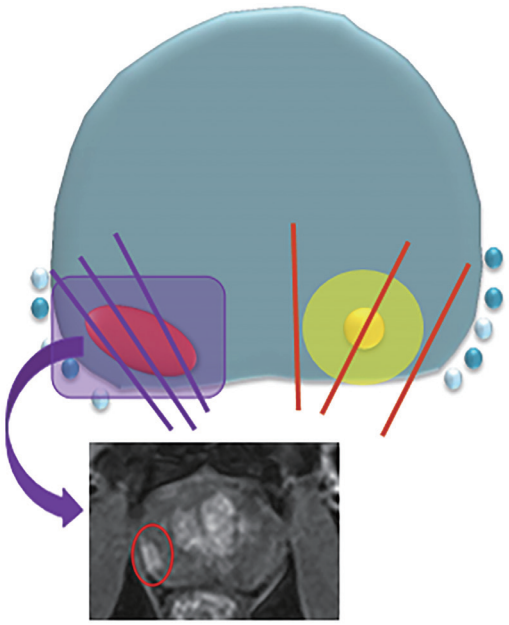

Figure 1 Illustration of targeted and systematic biopsy cores in relation to prior multi-parametric prostate MRI. Graphic representation of targeted cores (purple line) of prostate tumour (red oval) demonstrated on pre-biopsy MRI (red circle). Second prostate tumour (yellow circle) invisible to imaging detected on non-targeted systematic cores (red line).

Table 1 Value of systematic sampling in an mp-MRI targeted prostate biopsy strategy

For
Added yield of clinically significant cancer detection rate in non-targeted systematic biopsy
mp-MRI invisible prostate cancer
Final histopathology grade disparity
Against
Higher yield of clinically insignificant cancer
mp-MRI targeted biopsy alone provides a higher yield of significant and low yield of insignificant cancer
Increased biopsy related toxicity
Cost and reporting impact of additional non-targeted cores
Utility in men with a negative prior prostate biopsy

in the cohort of men with MRI-visible lesions. Despite improvements in mp-MRI performance and standardised radiological reporting, a significant fall in radiologically invisible csPCa, subsequently confirmed on systematic biopsy, has not occurred (5-8).

Research has now focused on the true clinical utility of an additional non-targeted systematic biopsies when performed alongside an mp-MRI targeted prostate biopsy during the same biopsy session (*Figure 1*). In this article we summarise the current evidence base for and against a "combined biopsy" approach (*Table 1*), calculating the marginal gains in cancer detection rate in each strategy.

Evidence against a combined mp-MRI targeted and non-targeted biopsy approach

csPCa detection rate in mp-MRI targeted prostate biopsy alone

The strongest evidence against a combined biopsy strategy is born from the results of mp-MRI targeted prostate biopsy results in the detection of csPCa. The current literature reports the detection rate of csPCa and clinically insignificant prostate cancer (ciPCa) in mp-MRI targeted biopsy as 25–62% and 5.6–23%, respectively (*Table 2*) (5,7-14).

Kasivisvanathan and colleagues' PECISION trial demonstrated mp-MRI targeted prostate biopsy improved the cancer detection rate of Gleason ≥3+4 disease (39%), whilst reducing the detection of insignificant (Gleason 3+3) cancer (23%) (2). Further, the detection of insignificant disease was significantly higher in the systematic biopsy comparator arm (22% *vs.* 9%; P<0.001) (12). The MRI-FIRST randomized trial by Rouviere and colleagues confirmed similar favourable detection rates of csPCa (32.3%) and a lower rate of insignificant prostate cancer detection (5.6% *vs.* 19.5%; P<0.0001) in targeted cores (5). Finally, Porpiglia *et al.*'s randomised study, utilizing transperineal prostate biopsy, confirmed targeted biopsy had a csPCa detection rate of over 41% (7). In these studies, the higher rate of clinically insignificant disease in systematic biopsy compared to targeted biopsy is considered sufficient evidence to preclude the performance of simultaneous systematic sampling.

Beyond the randomised controlled trial setting, Miah and colleagues' prospective cohort study of transperineal image-fusion biopsy reported similarly high rates of csPCa (48.4%) and a low rate of insignificant disease (15.1%) detection (15). Of clear methodological distinction from aforementioned studies, the non-targeted biopsy performed in this study did not anatomically overlap in areas with targeted core sampling (10). Thus, preventing the duplication of

Table 2 Absolute cancer detection rates of clinically significant and clinically insignificant prostate cancer in mp-MRI targeted prostate biopsies

Author	Year	N	Study design	Pre-biopsy MRI	Prostate biopsy approach	Form of targeted biopsy	csPCa in mp-MRI targeted biopsy, % [n]	ciPCa in mp-MRI targeted biopsy, % [n]	Comments
Elkhoury *et al.* (PAIREDCAP) (9)	2019	300 (248*)	Paired-control trial	mp-MRI 3T	TRPB	C or F	62% [154]	NR	All biopsy naïve
Miah *et al.* (10)	2019	640	Prospective cohort study	mp-MRI 3 T	TPB	F	48.4% [310]	15.1% [91]	Prior prostate biopsy not excluded. Likert score used for biopsy decision. Targeted only in some men
van der Leest *et al.* (4M) (8)	2019	626	Prospective cohort study	mp-MRI 3T	TRPB	IB	25% [159]	14% [88]	All biopsy naïve
Mannaerts *et al.* (11)	2019	225	Prospective cohort study	mpMRI	TRPB	F	44% [113]	8% [21]	Likert score used for biopsy decision
Rouviere *et al.* (MRI-FIRST) (5)	2018	335 (251*)	Randomised controlled trial	mp-MRI 3 T or 1.5T	TRPB	C	32.3% [81]	5.6%	Systematic biopsy in all men regardless of mp-MRI results
Kasivisvanathan *et al.* (PRECISION) (12)	2017	252	Randomised (non-inferiority) trial	mp-MRI 3 T or 1.5T	TRPB	C or F	39% [95]	23% [9]	mp-MRI targeted compared to systematic biopsy
Porpiglia *et al.* (7)	2017	107	Randomised controlled trial	mpMRI 1.5T	TRPB or TPB	F	41.1% [44]	18.5% [10]	TRPB 67.0%, TP 32.1%
Siddiqui *et al.* (13)	2015	1,003	Prospective cohort study	mpMRI	TRPB	F	31.3% [314]	–	Excluded if no visible mp-MRI lesion
Filson *et al.* (14)	2016	1042 (825*)	Prospective cohort study	mpMRI	TRPB	F	27.7% [229]	15.8% [131]	Prior prostate biopsy not excluded

*, number of men who proceeded to prostate biopsy of any form. CDR, Cancer detection rate; csPCa, clinically significant prostate cancer (Defined as Gleason ≥3+4 or Gleason Grade Group 2); ciPCa, clinically insignificant prostate cancer; TRPB, transrectal prostate biopsy; TPB, tranperineal prostate biopsy; C, cognitive; F, fusion; IB, in-bore; NR, not reported.

reported csPCa in systematic cores performed in known regions of interest already sampled by prior targeted cores. Furthermore, van der Leest *et al.*'s prospective study, in which only biopsy-naïve men underwent an in-bore mp-MRI targeted transrectal biopsy, reported a 25% csPCa and a 14% ciPCa detection rate (8). Figures from both of these studies are highly promising for the replication of such favourable targeted csPCa detection rates in routine clinical practice.

Anatomically, mp-MRI targeted biopsy is superior to systematic biopsy at detecting anterior and apical tumours (16). These are frequently missed on systematic TRUS prostate biopsy (17). It is worth noting that the current literature does not place preference on the form of targeted biopsy (i.e., targeted software fusion versus targeted cognitive fusion) when assessed in terms of csPCa detection rate (5,8,10,12,18). This is supported by the findings of high-level evidence from the FUTURE randomised controlled trial, which demonstrated no significant difference in csPCa detection when comparing targeted software fusion and targeted cognitive fusion biopsies in men with a previous negative systematic non-targeted prostate biopsy (18).

Men with a prior negative biopsy

The detection of csPCa in men with a prior negative prostate biopsy can be significantly increased with MRI-targeted prostate biopsy (17,19). Sonn and colleague's demonstrated a 20% (21/105) csPCa detection rate using mp-MRI targeted biopsy in men with a prior negative biopsy but continued suspicion secondary to elevated PSA (19).

Furthermore, Patel *et al.* evaluated the utility of systematic biopsy alongside fusion targeting and found that a prior negative prostate biopsy was significantly associated with the absence of clinically significant cancer in the non-targeted systematic cores (OR 0.46; 95% CI, 0.21–0.99; P=0.046) (20). Whilst no consensus exists on the role of a combined biopsy strategy in men with a prior negative biopsy status, there is growing evidence non-targeted cores in this setting offer little clinical utility (20).

Morbidity and cost of additional non-targeted systematic cores

Evidence from patient reported outcome measures in template-mapping trials, supports the notion that additional cores performed in a prostate biopsy pathway can be detrimental to post-biopsy urinary flow, genitourinary and sexual function (21). In contrast, the reported complication rate of local anaesthetic or sedation for targeted transperineal prostate sampling is low, with a reported post-biopsy urinary retention and sepsis rate of less than 1% (22).

However, a systematic review by Loeb *et al.* reported greater biopsy related pain with increasing number of cores performed (23). In addition, there is evidence that suggests that patient-reported outcome measures (PROMS), in particular urinary flow and sexual function, are persistently poorer in men who undergo prostate biopsies with a high median number of cores (21,24). Reducing the overall number of cores obtained by limiting non-targeted systematic cores may offer improvements in post-biopsy genitourinary functional outcomes without sacrificing oncological outcomes.

Compared to systematic TRUS biopsy, targeted biopsy using image fusion has been proven to be cost-effective (25). This is despite concerns over higher initial pathway set-up costs and implementation (25). Venderink and colleagues reported the incremental cost-effectiveness ratio of MRI-TRUS image fusion over systematic TRUS biopsy to be $1,470 per quality-adjusted life year gained; thus, deeming image fusion cost-effective (25).

Performing additional non-targeted cores in a targeted biopsy pathway does directly increase the histopathology cost per case by an estimated £112.79/$146.81 (26). In addition, the downstream effects are an increase the technical reporting load on pathologists and a wider clinical reviewing burden on multi-disciplinary meetings.

Evidence for a combined mp-MRI targeted and non-targeted approach

Added value of a csPCa detection in combined biopsy

The additional diagnostic yield of csPCa detection by performing a non-targeted systematic biopsy in addition to an mp-MRI targeted biopsy is reported to be 1.3% to 11% (*Table 3*) (5,8-11,14,27). A combined biopsy strategy may refer to mp-MRI targeted cores in addition to either sectoral templating or 12-core systematic TRUS. The Ginsburg Study Group on Enhanced Prostate Diagnostics have supported a sectoral templating approach since 2013 (28). On the premise that preferential targeting of the peripheral zones leads to the avoidance of the inherent oversampling of template-mapping sampling and the under-sampling of systemic TRUS in isolation (28).

However, MRI-FIRST, the multicenter, paired

Table 3 Absolute cancer detection rates of clinically significant cancer in mp-MRI targeted and systematic prostate biopsies

Author	Year	n	Study design	Pre-biopsy MRI	Prostate biopsy approach	Form of targeted biopsy	csPCa in targeted biopsy, % [n]	csPCa in systematic biopsy, % [n]	csPCa in combined, % [n]	Value add of combined biopsy, % [n]	Comments
Jayadevan *et al.* (PAIREDCAP) (9)	2019	300 [248*]	Paired-control trial	mp-MRI 3 T	TRPB	C or F	62% [154]	60% [151]	70% [178]	+11% [27]	All biopsy naïve
Miah *et al.* (10)	2019	640 [358*]	Prospective cohort study—targeted biopsy followed by limited systematic	mp-MRI 3 T	TPB	F	48.4% [310/640]	17.9% [64/358]	49.7% [319/640]	+ 1.3% [9/640]	Prior prostate biopsy not excluded. Likert score used. Targeted only in some men
van der Leest *et al.* (4M) (8)	2019	626	Prospective cohort study—targeted biopsy followed standard 12-core TRPB	mp-MRI 3T	TRPB	C	25% [159]	23% [146]	48% [301]	+7% [21/317]	All biopsy naïve
Mannaerts *et al.* (11)	2019	225	Prospective cohort study—standard 12-core TRPB followed by targeted biopsy	mp-MRI	TRPB	F	44% [113]	43% [110]	52.4% [118]	+ 8% [9]	Likert score used.
Rouviere *et al.* (MRI-FIRST) (5)	2018	335 [251]	Randomised controlled trial (paired diagnostic)—standard 12-core TRPB followed by targeted biopsy	mp-MRI 1.5T or 3T	TRPB	C	32.3% [81]	29.9% [75]	37.5% [94]	+ 5.2% [4.8]	Systematic biopsy in all men regardless of mp-MRI results
Filson *et al.* (14)	2016	1042 [825^{T}]	Prospective cohort study—standard 12-core TRPB followed by targeted biopsy	mp-MRI	TRPB	F	24% [199]	27.8% [229]	35% [289]	+ 7.27% [60]	Prior prostate biopsy not excluded

Marginal gains (added value) of combined biopsy. *, number of additional non-targeted systematic biopsy performed. ^{T}, number of patients with region of interest on mpMRI who underwent both biopsy. CDR, Cancer detection rate; csPCa, clinically insignificant prostate cancer (defined as Gleason ≥3+4 or Gleason Grade Group 2); TRPB, transrectal prostate biopsy; TPB, transperineal prostate biopsy; C, cognitive; F, fusion.

diagnostic study by Rouviere and colleagues has provided the first high-level data utilizing a combined TRUS-biopsy strategy (MRI-targeted followed by 12-core systematic) (5). In their study, 251 men underwent combined prostate biopsy; the csPCa detection rate was 29·9% (95% CI, 24.3–36.0) for systematic biopsy and 32.3% (95% CI, 26.5–38.4) for targeted biopsy. csPCa would have been missed in 5.2% of cases if systematic biopsy had not been performed, and in 7.6% if targeted biopsy was not performed. csPCa detection rates were improved when both biopsy methods were combined. However, targeted biopsy detected significantly more grade group ≥3 tumours and significantly fewer grade group 1 tumours.

Elkhoury and colleagues' recently-published PAIREDCAP trial was paired-cohort study of 248 biopsy-naïve men who underwent a 12-core systematic biopsy followed by two MRI targeted biopsies (targeted cognitive fusion and targeted software fusion) during the same session (9). csPCa was detected in 47% of targeted cognitive fusion biopsies, 54% of targeted software fusion biopsies, and 60% of biopsies obtained via systematic sampling. However, a combined approach resulted in maximal detection, with a 70% (178/248) csPCa detection rate, an additional diagnostic yield of 11% (9).

Using a similar combined targeted and 12-core TRUS approach, Filson and colleagues' study of 825 men reported csPCa in 24% and 27.8% of the non-targeted and targeted prostate biopsies, respectively (14). The combination of systematic and targeted biopsies detected more csPCa (n=289) than targeting (n=229) or systematic biopsy alone (n=199). 60 patients were found to have csPCa on systematic biopsy that would have been missed by targeted biopsy alone. Additionally, one in eight men without a suspicious lesion on mpMRI were diagnosed with csPCa via systematic biopsy.

Van der Leest *et al.*'s study utilized an in-bore MRI-guided transrectal biopsy followed by a 12-core TRUS (8). The authors reported a 7.0% (21/317) additional csPCa detection rate when using a combined biopsy approach. Other studies utilizing purely transperineal prostate biopsy have reported the additional diagnostic yield of csPCa at 1.3% (10).

The additional yield of csPCa detected in a combined strategy varies widely across the literature. However, the above studies suggest a significant proportion of csPCa is missed when only a mp-MRI targeted biopsy is performed. The level of acceptable of "missed csPCa" in these pathways is a wider debate yet to gain international consensus.

mp-MRI invisible disease and inter-observer reproducibility

A major limitation of exclusive mp-MRI targeted biopsy is the notion of patients harboring mp-MRI-invisible disease. In men with no identifiable region of interest on mp-MRI, targeted biopsy is not performed and "invisible" disease would otherwise go undetected (29). The PROMIS trial demonstrated that mp-MRI had a sensitivity of 93% and negative predictive value of 89% for predicting csPCa (defined as Gleason ≥4+4 or MCCL ≥6 mm) (1). A recent meta-analysis on the topic reported the median mp-MRI negative predictor value was 82.4% (IQR, 69–92.4%) (29). Unsurprisingly, negative predictor value significantly decreased when baseline cancer prevalence increased (29). mp-MRI invisible disease remains a significant clinical concern amongst urologists in routine clinical practice (30).

Filson's group identified that 12% of biopsy naïve men with no ROI who underwent a systematic biopsy had clinically significant disease (14). Le and colleagues' study of 112 whole-mounted prostatectomy specimens detected csPCa in 28% of cases, cancer that was invisible to expert reported mp-MRI (31). Furthermore, Chung *et al.* retrospectively reviewed 213 radical prostatectomy specimens matched to prior mp-MRI reports (32). The group defined "invisible" prostate cancer was as those graded PIRADS 1 or 2, or those with no MRI-visible region of interest. The group reassuringly found 76.1% of mp-MRI invisible cancer was clinically insignificant disease. However, 6.6% (n=20) of those with negative MRI were found to have ≥ Gleason 8 disease (31).

In van der Leest and colleagues' study an additional 21 men were diagnosed with csPCa using a combined biopsy strategy (8). However, in 20 of these 21 additional cases the ROI was present on pre-biopsy mp-MRI. Thus, only a single patient (<1%) had mp-MRI invisible cancer detected on a non-targeted systematic biopsy (8).

Persistence of MRI invisible disease has limitations for mp-MRI as a triage biopsy tool in biopsy naïve men. The answer to this may lie in combining MRI-derived parameters (e.g., MRI-prostate volume, PIRADS 1 or 2) in addition to clinical variables (e.g., age, ethnicity) (33). Such modelling produces a binary (yes/no) outcome to the risk of csPCa (33). At present it should be noted, the addition of such modelling into mp-MRI triage has only supported a significant reduction in false-positive rates (33).

Finally, with regard to agreement on mp-MRI ROI score (PIRADS or LIKERT), this has suffered from low inter-observer reproducibility (34). One study found even

experienced radiologists, using PIRADS version 2, had poor agreement in the peripheral zone for features relating to diffusion weighted imaging (k=0.53–0.61) (34). With low inter-observer reproducibility, an MRI interpreted as having an ROI by one radiologist may be graded as "negative" by another, failing to trigger a targeted biopsy. In this example case, detection would only be possible via systematic biopsy.

Final histopathology grade disparity

There is some concern that exclusive targeted sampling may underestimate whole gland disease status and thus impact the downstream treatment modality choice by patients (31,35,36). Muthigi and colleagues reviewed the whole mount pathology of 1,003 serial patients in whom patients were upgraded in non-targeted systematic cores alone to csPCa in 13.5% (n=135). Only 1.1% (n=11) resulted in the identification of high-risk disease (Gleason ≥8) (36). When detailing failure of targeted biopsy to detect this disease the authors' concluded that MRI invisible disease, operating clinician technique failure and intra-lesion Gleason heterogeneity were all significant (36).

Furthermore, when reviewing whole-gland prostatectomy histopathology Siddiqui and colleagues reported that the sensitivity of targeted prostate biopsy in detecting Gleason ≥7 rose from 77% (95% CI, 67–84%) to 85% (95% CI, 76–91%) when a combined strategy was utilized (13).

Finally, the ability to accurately characterize cancer morphology, in particular Gleason 4 subtypes on targeted biopsy alone has been questioned (37). The presence of Gleason pattern 4 cribriform tumours is associated with increased cancer specific mortality and is an adverse independent predictor of metastasis-free survival (37,38). Truong and colleague's, re-reviewed 694 positive cores for pattern 4 subtypes. The group concluded that a combined biopsy over a targeted only strategy increased absolute cribriform pattern detection by 8.5% (37.1% *vs.* 28.6%) (35). Awareness of the presence of such morphology has notable downstream effects on the treatment choices and associated risks presented to patients.

Conclusions

We are yet to reach a stage where non-targeted systematic prostate biopsy can be routinely omitted in mp-MRI targeted prostate biopsy pathways. Research should focus on improving the accuracy of mp-MRI, prostate biopsy techniques and in identifying those men likely to most benefit from adding non-targeted systematic biopsies. Such strategies may help future urologists reduce the burden of non-targeted cores in modern mp-MRI prostate biopsy pathways.

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Footnote

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