



Review

MRI-informed prostate biopsy: What the radiologist should know on quality in biopsy planning and biopsy acquisition

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ABSTRACT

Quality is currently recognized as the pre-requisite for delivering the clinical benefits expected by magnetic resonance imaging (MRI)-informed prostate biopsy (MRI-i-PB) in patients with a suspicion for clinically significant prostate cancer (csPCa). The “quality chain” underlying MRI-i-PB is multidisciplinary in nature, and depends on several factors related to the patient, imaging technique, image interpretation and biopsy procedure. This review aims at making the radiologist aware of biopsy-related factors impacting on MRI-i-PB quality, both in terms of biopsy planning (threshold for biopsy decisions, association with systematic biopsy and number of targeted cores) and biopsy acquisition (biopsy route, targeting technique, and operator’s experience). While there is still space for improvement and better standardization of several biopsy-related procedures, current evidence suggests that high-quality MRI-i-PB can be delivered by acquiring and increased the number of biopsy cores targeted to suspicious imaging findings and perilesional area (“focal saturation biopsy”). On the other hand, uncertainty still exists as to whether software-assisted fusion of MRI and transrectal ultrasound images can outperform cognitive fusion strategy. The role for operator’s experience and quality assurance/quality control procedures are also discussed.

1. Introduction

Over the last years, magnetic resonance imaging (MRI) of the prostate has gained a central role in directing prostate biopsy decisions in patients with clinical suspicion of prostate cancer. Given a negative predictive value > 90%, a negative MRI scan can avoid up to 30% of unnecessary biopsies in the typical population of biopsy-naïve patients with a disease prevalence around 30–40%, with the additional advantage of reducing the overdiagnosis of clinically insignificant prostate

cancer (ciPCa) [1–2]. While prompting biopsies with still a suboptimal positive predictive value [3], prostate MRI is helpful in identifying and localizing suspicious lesions to be sampled with targeted biopsies, and in turn improving the detection ratio of clinically significant prostate cancer (csPCa) compared to systematic biopsy alone [1]. Proper biopsy planning (e.g., choice of the number of targeted cores) and biopsy acquisition (e.g., choice of the biopsy route and technique) are key processes in the diagnostic pathway centered on MRI-informed prostate biopsy (MRI-i-PB).

Abbreviations: ciPCa, Clinically insignificant prostate cancer; C-MRITB, Cognitive magnetic resonance imaging target biopsy; csPCa, Clinically significant prostate cancer; EAU, European Association of Urology; ESUI, European Association of Urology, Imaging Section; ESUR, European Society of Urogenital imaging; F-MRITB, Fusion magnetic resonance imaging target biopsy; IN-MRITB, In-bore magnetic resonance imaging target biopsy; ISUP, International Society of Urogenital Pathology; MRI, Magnetic resonance imaging; MRI-i-PB, Magnetic resonance imaging-informed prostate biopsy; MRITB, Magnetic resonance imaging target biopsy; PI-QUAL, Prostate imaging quality; PI-RADS, Prostate imaging reporting and data system; PSA, Prostatic specific antigen; PSAD, Prostatic specific antigen density; QA, Quality assurance; QC, Quality control; TPR, Transperineal route; TRR, Transrectal route; TRUS, Transrectal ultrasound.

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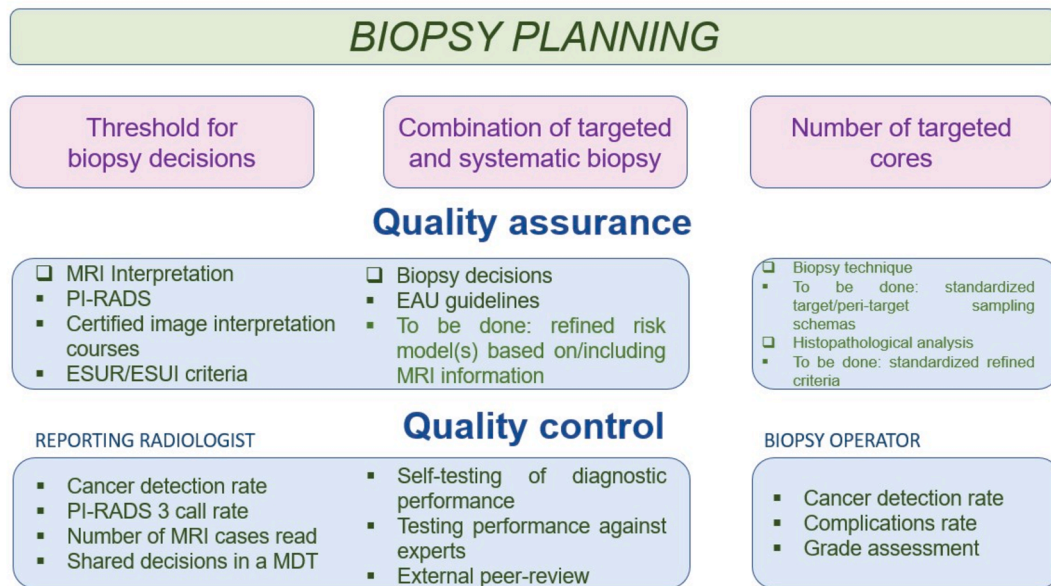


Fig. 1. Main quality assurance and quality control checkpoints for biopsy planning. EAU = European Urology Association; ESUI = European Association of Urology, Imaging Section; ESUR = European Society of Urogenital imaging; MDT = multidisciplinary team; MRI = magnetic resonance imaging; PI-RADS = prostate imaging reporting and data system.

Indications to prostate MRI, and impact on biopsy decisions against patient risk stratification are a matter of an evolving debate [4–5]. It is commonly accepted that the expected benefits of an MRI-i-PB-centered diagnostic pathway can be delivered only if a “quality chain” exists, including radiologists, urologists, pathologists and any other component of a multidisciplinary team involved in patient management (from diagnosis to treatment) as well as in assuring the robustness of the whole process (e.g., by accreditation and audit) [6–7]. As recently emphasized by Barrett et al. [8], “quality” in prostate MRI depends on two distinct processes, i.e., quality assurance (QA) and quality control (QC). QA pertains to general processes serving as a reference for ensuring high quality and standardization, as exemplified by the Prostate Imaging Reporting And Data System (PI-RADS) [9] or guidelines such as those provided by the European Association of Urology (EAU) [10] or the International Society of Urological Pathology (ISUP). QC refers to the procedures to objectively measure whether quality standards have been met in a certain clinical setting, (e.g., audit and certification) [8].

As discussed in previous works [8,11], there are several factors impacting on MRI-i-PB quality, including patient-related issues, MRI hardware and technique, MRI protocol (multiparametric versus biparametric), image quality, radiologist’s interpretation, biopsy and pathological analysis. The biopsy level is associated with specific quality issues which the radiologist should be aware of in order to interact proficiently when sharing biopsy decisions or implement QA/QC processes in a multidisciplinary team.

This review will focus on the factors impacting on the quality of biopsy planning and acquisition in the MRI-based primary diagnosis of prostate cancer. As the review is meant to meet the radiologist’s needs, technical details on MRI-i-PB will not be covered as they can be found elsewhere (e.g., sampling schemes, required equipment or analgesia) [12]. Readers can refer to previous works also for the topic of quality in histopathological analysis of biopsy samples as an additional quality-related factor impacting on MRI-i-PB [8].

2. Biopsy planning

Biopsy planning refers to the sampling strategy chosen for maximizing the expected benefits of MRI-i-PB, assuming a certain acquisition technique (see below). The most relevant choices pertain to: i) whether

performing systematic biopsy; ii) which MRI finding should be the object of targeted biopsies; iii) how many cores per target should be taken. These choices will be presented by emphasizing current MRI-i-PB limitations since they indicate the directions for further improvement in quality (Fig. 1).

2.1. Threshold for biopsy decision

The threshold for biopsy decision coincides with the degree of suspicion for csPca on prostate MRI. Despite suboptimal inter-reader agreement, the PI-RADS version 2.1 guidelines remain the main QA reference in this setting, as they provide standardized interpretation rules [9,13]. However, even when using the PI-RADS guidelines, there is currently a high rate of false-positive targeted biopsies, which is a major problem in the current MRI-i-PB diagnostic pathway. As an example, per-lesion/per-patient prevalence of csPca on targeted biopsy is 20 and 13%, and 52 and 40% only in PI-RADS 3 and PI-RADS 4 category, respectively [3,14]. There is intense research on how to refine biopsy thresholds balancing the need for high sensitivity (biopsies to be done) and acceptable specificity (biopsies that could be avoided) (e.g., by integrating MRI results with clinical information, or using risk calculators including MRI information to build risk prediction). It has been shown that merging biomarkers, risk calculators and MRI findings leads to higher performance than their use as stand-alone tools [15]. The easiest and most popular strategy aims at adjusting the PI-RADS threshold with the prostate specific antigen level density (PSAD), reserving biopsy to patients with a PI-RADS ≥ 3 lesion and elevated PSAD (e.g., ≥ 0.15 ng/mL/mL) [10,14].

This approach is effective in reducing unnecessary biopsies triggered by false-positive MRI findings, especially PI-RADS 3 lesions, which harbor cancer in only 17% of cases [16]. Since the PI-RADS 3 call rate depends on image quality and reader’s experience, it represents an ideal QC marker for assessing the quality of radiologist’s interpretation, and in turn decision for MRI-i-PB [8]. Assuming a prevalence of csPca of 40%, the average PI-RADS call rate is around 17%, with expert centers showing a lower proportion (<10%) [17]. Those values represent a benchmark for the purpose of quality assessment, though the exact reference standard for QC processes has not been defined yet.

Overall, the issue of biopsy threshold is still an open question that

Table 1

Overview of relevant studies dealing with the optimization of the number of focal saturation biopsy cores taken from each magnetic resonance imaging (MRI) target. CDR = cancer detection rate; csPca = clinically significant prostate cancer; ciPca = clinically insignificant prostate cancer; PI-RADS = Prostate Imaging reporting and Data System.

	Study design	Biopsy technique/Number of targeted cores under analysis	Main results
Lu et al., 2019 [34]	Retrospective inclusion of 744 men (biopsy-naïve patients, prior negative biopsy and active surveillance) receiving 2 targeted samples or 5 targeted samples	Software-assisted fusion MRI/2 versus 5	- Five cores-sampling missed substantially fewer cancers compared to two cores-sampling
Zhang et al., 2019 [35]	Retrospective inclusion of 330 men (active surveillance and prior negative biopsy)	Cognitive MRI-targeting/5	- Increasing the number of biopsy core samples from 1 to 3/per target and from 3 to 5/per target increased the detection rate of clinically significant cancer by 6.4% and 2.4%, respectively - Target yield for 5 cores was 35%
Ploussard G et al., 2020 [36]	Prospective inclusion of 478 men who underwent radical prostatectomy	Software-assisted fusion MRI/<2 versus ≥ 5	- The minimal number of cores to reduce upgrading risk at radical prostatectomy was 4 in PI-RADS 3, and 3 in PI-RADS 4–5 cases
Hansen NL et al., 2020 [38]	Prospective inclusion of 487 men	Software assisted transperineal MRI/2 versus 4 versus 10–20 cores including sectors adjacent to the target versus 14-core ipsilateral target biopsy versus combined target and systematic 20–26 cores biopsy	- 10–20 cores focal saturation biopsy comparable to target + systematic biopsy (CDR 91%) - 4 cores target biopsy can suffice for large, highly suspicious lesions (CDR 76%)
Tracy et al., 2021 [37]	Prospective enrollment of 104 men (82% with prior biopsy)	Software-assisted fusion MRI/5	- Incremental value in detecting csPca from 26% to 44% to 52% when comparing the first, third, and fifth biopsy cores in men with PI-RADS > 3 lesions.
Lahoud et al., 2021 [39]	Retrospective monocentric inclusion of 254 men	MRI-ultrasound fusion or cognitive registration using a brachytherapy grid, targeted and perilesional biopsies/Median of 5 cores per-target	- For PI-RADS 4 and 5 lesions, perilesional biopsy in addition to targeted biopsy detected 9% more csPCs, at the cost of an increased 4% overdiagnosis of iPCa. -For PI-RADS 3 lesions, perilesional biopsies did not increase the CDR for csPca
Tschiderwahn et al., 2021 [40]	Retrospective inclusion of 213 men	Transperineal MRI/TRUS-fusion biopsies (target biopsy e target saturation) compared with extended systematic biopsies (SBs)/Median of 4 cores for target biopsy, 9 cores for target saturation and 24 cores for systematic biopsy	- The CDR was greater for target saturation (99%) than target biopsy (87%) and systematic biopsy (82%).
Saner et al., 2023 [41]	Prospective inclusion of 170 men	Men were randomized to conventional target biopsy with 4 cores (n = 85) versus target saturation with 9 cores (n = 85)	- Comparable CDR.

should be put into the evolving context of how much prostate MRI can contribute to stratify patients' risk of csPca in combination with clinical data [4]. We believe that, in line with previously suggested [8], image interpretation workshops and continuing professional development programs are fundamental as QA in establishing a confident use of the PI-RADS [8], and should be attended by less experienced radiologists to be qualified to read prostate MRI. In our experience, the related QC level is achieved by performing a regular retrospective check of key indicators (cancer detection rate, false-positives rate and PI-RADS 3 calls) established by the prostate multidisciplinary team. Additionally, urogenital radiologists are asked to re-read slots of past cases. After that, original reports and biopsy results are unblinded for critical comparison. While driven even by research purposes, similar models can reasonably be adapted even outside the academic context.

2.2. Role of combined systematic biopsy

Prostate MRI misses up to 8.8% of csPca [18]. The so-called MRI-invisible lesions usually correspond to csPC with smaller size and lower ISUP grading group (typically ISUP 2) [11], though they can include aggressive histological variants such as cribriform tumors, ductal adenocarcinoma [11,16,19], and more aggressive molecular profiles [18]. Additionally, the high sensitivity of prostate MRI for the detection of csPca cannot be easily replicated outside high-volume centers where readings are usually performed by less experienced readers [2,20]. A recent consensus document by the European Society of Urogenital Radiology (ESUR) and European Society of Urology Imaging section (ESUI) [19] provides strict criteria for qualifying a radiologist as an “expert” (e.g., reading a minimum of 200 cases per year and having an

experience of at least 1,000 prostate MR cases). In this context, “experience” implies dedicated training and participation to a multidisciplinary team for review, biopsy decision sharing, and acquisition of the required knowledge of the potential effects of false results, e.g., risk of inducing unnecessary biopsies. Other suggested QC processes for measuring the impact of image interpretation include self-performance tests, external peer review, and performance measurement against histopathological feedback and expert reading [19]. In the United States, the American College of Radiology established a pathway for being accredited as designated center for prostate MRI. According to these criteria, suitable radiologists are those having reported at least 150 MRI scans in prior 36 months [21].

Overall, while some guidelines suggest biopsy of only the region of interest (ROI) outlined on suspicious MRI findings [22], the EAU guidelines still recommend performing also systematic biopsy as a safety-net in biopsy-naïve patients, because its combination with targeted biopsy increases the cancer detection rate by retrieving csPca missed by MRI [10,18]. Systematic biopsy can be avoided only in clinical scenarios at higher risk such as previous negative biopsy, or rather low risk scenarios with negative MRI [10]. It has been recently suggested that systematic biopsy might be safely omitted even in patients with PI-RADS 5 findings [23].

2.3. Number of targeted cores

As mentioned, targeted biopsies of suspicious MRI findings could not contain csPca. There is increasing awareness that a few “false-positive” MRI targets are in fact false-negative biopsies, suggesting the need for repeat sampling in cases at higher clinical risk [24]. Explanations for this

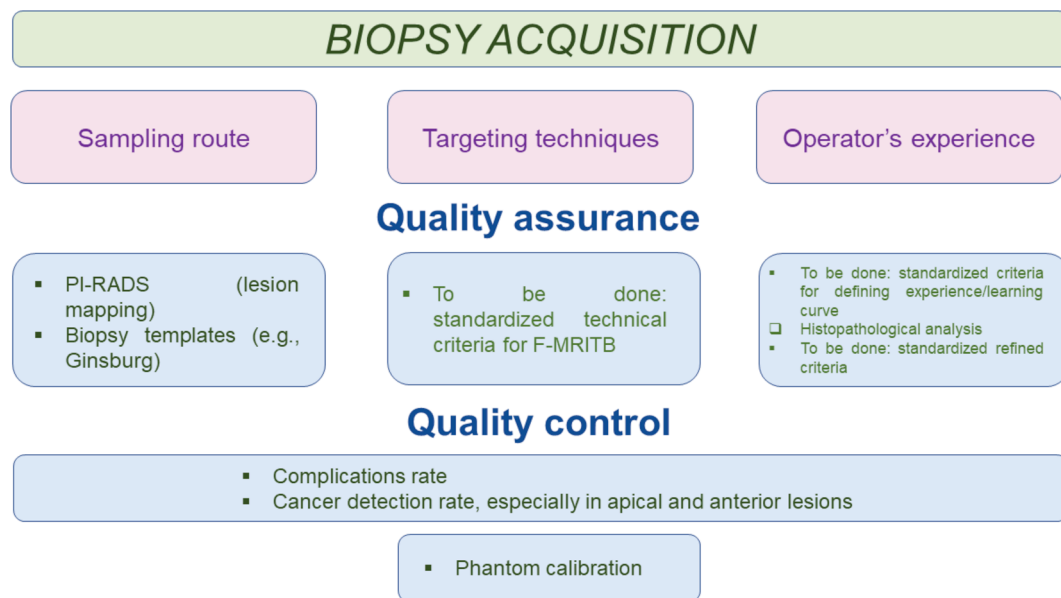


Fig. 2. Main quality assurance and quality control checkpoints for technical/operative aspects of biopsy acquisition. F-MRITB = software-assisted fusion magnetic resonance imaging targeted biopsy; PI-RADS = prostate imaging reporting and data system.

phenomenon include errors in targeting biopsy or issues in sampling areas that are difficult to access, especially with larger gland and/or small lesions [18,25]. Larger prostate volumes due to benign prostatic hyperplasia are also supposed to determine greater needle tip deflection, thus further reducing biopsy accuracy [26]. According to Schouten et al. [27], MRI-i-PB has limitations in detecting dorsolateral (58%) and apical (37%) lesions, whereas systematic cores peripheral to PI-RADS 4–5 lesions are often positive for csPCa despite negative targeted biopsy. Acquiring at least two cores from a suspicious ROI is a common strategy for reducing the risk of sampling errors, although csPCa can be missed in up to 22% of cases even when taking four targeted cores [8].

There is space for improvement also in the capability of MRI-i-PB to assess biological aggressiveness and tumor burden for the purpose of risk stratification. MRI can detect the index lesion in >90% of cases [28], and in turn guide biopsy to the target likely having the greatest biological relevance. However, it has been recently shown that the index lesion can be missed if corresponding to a high-grade MRI-invisible cancer, and that MRI can rather trigger targeted biopsy of co-existing visible lesions of lesser biological significance [18]. MRI also shows a well-known tendency to underestimate cancer volume [28–29], quantified by Priester et al. in 11 mm in diameter and threefold in volume on average [30]. Intraleisional biological heterogeneity is an additional problem as currently no validated systems can assist in sampling the most biologically relevant component of MRI-visible targets [31].

Definitive standardization in biopsy planning is lacking. However, growing evidence suggests that the best strategy to overcome the above issues is to concentrate the cores in proximity to the MRI lesion [32] performing the so-called “focal saturation biopsy” (e.g., by taking 3–5 cores from the ROI and the surrounding “penumbra” without a direct correlate on MRI) [8]. This strategy is in line with recent results showing that a systematic biopsy ipsilateral to a negative targeted ROI is most often positive for the detection of csPCa [33]. A summary of relevant studies in this field [34–41] is provided in Table 1. Of note, the only randomized controlled trial available found no differences between 4-core and 9-core targeted biopsies, though uneven distribution of csPCa prevalence and possibly underpowering (170 participants) could have affected the results [41]. Indeed, focal saturation was shown to detect 99% of csPCa [40] and has been prompted by the PI-RADS Steering Committee as the recommended approach for PI-RADS 4–5 lesions, using a 5-mm width penumbra [42]. Recently, Brisbane et al. [32]

suggested increasing the penumbra radius to 10 mm from the ROI’s surface to maximize cancer detection, as they found that 90% of positive biopsy cores were within this area. In this study, the prevalence of csPCa within the ROI was linked to the degree of MRI suspicion, as it was 50%, 60% and 74% for category 3, 4 and 5, respectively. Interestingly, Calio et al. [31] found that a 4-core focal saturation of the index lesion through transrectal fusion MRI-i-PB significantly decreased the risk of Gleason score and risk category upgrading on radical prostatectomy, suggesting that this approach minimized the impact of tumor heterogeneity. Of note, adding *peri*-target samples helps avoid grade migration bias performing histological adjustments during the examination of the biopsy, and better defining tumor volume for the purpose of surgery, focal treatment or a radiation therapy plan including focal boost [4].

From quality-center viewpoint, the above results emphasize the need for accurate outlining/contouring of the biopsy target, as this can significantly impact on the number of cores to be taken from the “umbra” of the ROI (3–5 according to the lesion volume) [8]) and related penumbra. In the center of most authors of this review, lesion outlining is provided in key images appended to the MRI documentation. Based on that, the urologist performing transperineal biopsy takes two cores from the lesion and two cores from the penumbra on a per-target basis. Additional samples are reserved to larger PI-RADS 5 lesions.

3. Biopsy acquisition

The procedural steps of MRI-i-PB acquisition include the choice of sampling route and targeting technique, as detailed below. The operator’s experience is an additional critical factor affecting the quality of MRI-i-PB that will be also discussed (Fig. 2).

3.1. Sampling route

Transperineal ultrasound-guided biopsy was first described in 1981 [11]. However, the ease of combined transrectal route (TRR) and systematic biopsy sampling limited its use to niche indications until recently (e.g., in patients who underwent rectal resection) [11]. The transperineal route (TPR) has gained popularity in parallel with increased awareness of the risk and magnitude of infectious complications associated to the inoculation of rectal flora into the prostate through the needle passage across the rectal wall when using the TRR

Table 2

Results from relevant studies comparing the transrectal route (TRR) and transperineal route (TPR) of prostate biopsy. CDR = cancer detection rate for clinically significant prostate cancer; C-MRITB = cognitive MRI targeted biopsy; csPCa = clinically significant prostate cancer; F-MRITB = software-assisted fusion MRI targeted biopsy; = magnetic resonance imaging; TPR = transperineal route; TRR = transrectal route.

Study design	Targeting technique	CDR		Additional main results
		TRR	TPR	
Pepe et al., 2017 [53]	TPR systematic biopsy (median 30 cores) combined with targeted F-MRITB along the TRR and TPR routes (median 4 cores)	46.7%	86.7%	- The TPR detected more smaller anterior cancers
Ber et al., 2020 [54]	F-MRITB	26%	42%	—
Hsieh et al., 2022 [49]	F-MRITB for the TPR and C-MRITB for the TRR route	36.5%	52.2%	—
Zattoni et al., 2022 [55]	C-MRITB and F-MRITB	35%	49%	- The TPR allowed better assessment of cancer grade and patient risk than TRR

[43]. Post-procedural prostatitis and urinary tract infections can translate into sepsis requiring hospitalization in 3 to 10% of patients undergoing TRR biopsy, while sepsis rates after TPR biopsy range between 0 and 0.11% [12]. Of note, there is no definitive evidence that reducing the number of transrectally acquired cores by sampling MRI targets only can reduce the risk of infection [43]. Thus, while the TRR remains the most common and easily implementable approach to MRI-i-PB [43], there is currently increasing consensus on abandoning it in favor of the TPR. The so-called “TREXIT” (transrectal-exit) strategy is supposed to provide the additional advantage of reducing or avoiding antibiotic prophylaxis [44], and in turn prevent the spread of bacterial resistance [11–12]. Recently, the NORAPP trial showed that the rates of infection were not higher in men who did not receive antibiotic prophylaxis before TPR biopsy compared to patients receiving it [45]. Not surprisingly, the EAU guidelines recommend TPR as the biopsy technique of choice [10]. Current techniques allowing TPR biopsy in an outpatient setting under local anesthesia [46] are expected to favor a more widespread adoption of this approach.

A second major argument in favor of the TPR in the MRI-i-PB era is a better capability to sample the anterior prostate or apex, which are usually more difficult to visualize and target with the TRR [11]. Those areas represent the most frequent site of nonpalpable prostate lesions [47], with anterior cancer being the only site of disease in 9.2% of patients undergoing prostate biopsy [48]. Special needle guides developed to sample the anterior or apical prostate through the TRR are not popular and at risk of overdeflection of the needle [49]. Studies in patients with previous negative TRR ultrasound-guided systematic biopsy and persistent clinical suspicion of csPCa showed that most cancer foci found by a subsequent TPR biopsy were anterior or apical in location [11]. This emphasizes the need for careful lesion localization when reporting prostate MRI, (e.g., using the 41-sectors map provided by the PI-RADS guidelines) [9], and reliable targeting technique as discussed below.

While a recent metaanalysis [50] showed comparable pooled sensitivity and specificity for the detection of csPCa using software fusion biopsy (0.81 versus 0.80 and 0.99 versus 0.95, respectively), results from different studies by Tu et al. [51], Rai et al. [52] or individual series [49,53–55] suggest that the TPR outperforms TRR in terms of cancer detection rate at target biopsy, regardless of the targeting strategy (software fusion, cognitive or in-bore) (Table 2). Even when assuming comparable cancer detection rate, the TPR is associated to fewer complications such as fever or rectal bleeding compared to the TRR [56]. Of note, the possibility of using larger needle size (e.g., 16 gauge versus 18 gauge) has been advocated as an additional promoter of increased cancer detection rate when using the TPR [57]. A larger core size compared to the TRR is supposed to provide a more extensive sampling

of the gland and facilitates histopathological analysis. Notably, core integrity and length might represent an ideal QC marker for assessing the quality of MRI-i-PB [8].

The mainstay of QA when selecting the TRR or TPR is the use of biopsy templates allowing standardized and even systematic sampling of the prostate for the purpose of minimizing human error and provide precise localization of cancer foci [58]. While a detailed review of different biopsy templates can be found elsewhere [11,58], Table 3 summarizes the main categories of biopsy templates available at present [11–12,59–60]. Concerning the TPR, the Ginsburg biopsy protocol has been proposed by a consensus group in 2013 to optimize the number of systematic cores in view of the balance between diagnostic accuracy and risk of complications (Fig. 3) [11]. Indeed, the TPR is not devoid of its own complications such as transient erectile dysfunction or acute urinary retention, with risk rising when a larger number of cores is acquired, for example using the Barzell template [11]. Additionally, the Ginsburg protocol specifically accounts for imaging information as it recommends directing two target biopsies to lesions found on prostate MRI before performing systematic sampling [61]. In a work by Radtke et al. [62] the use of this template achieved 97% detection of csPCa with a median of 28 cores on a per-patient basis, and no major complications. A team from the Imperial College London proposed a biopsy template more deeply informed by prostate MRI results [63], as the presence of MRI targets in the peripheral zone (PZ) or transitional zone (TZ) impacts on the remaining sampling template. This model emphasizes the impact that reliable MRI interpretation can have on the biopsy technique.

It should be noted that there is still no consensus as to which biopsy template should be preferred or better integrates with MRI-derived information, and that there is great variability in practices across different institutions. This suggests that quality in MRI-i-PB should be reasonably the consequence of regular institutional QC audits assessing whether a certain practice (TRR or TPR) translates into acceptable cancer detection (possibly validated against radical prostatectomy histopathology) and complications rates [8]. We believe that the TPR should be privileged wherever possible as the reference sampling route, and that complications rate should be equal or lower than those expected from largely validated methods such as the Barzell template or Ginsburg protocol.

3.2. Techniques for targeted sampling

Once prostate MRI has been performed, there are three main techniques for directing subsequent MRI target biopsy (MRITB), depending on the type of real-time imaging guiding the procedure, and the way native MRI images are combined with real-time imaging. These different approaches are in-bore MRITB (IB-MRITB), and fusion technique,

Table 3

Popular schemes for performing systematic prostate biopsy to be associated with targeted biopsy. Although none is clearly preferred, they act as quality assurance benchmarks for prostate biopsy technique. CZ = central zone; PZ = peripheral zone; TZ = transition zone.

	Biopsy template	Systematic biopsy protocol	Median number of systematic cores	Advantages	Disadvantages
Transrectal route	Vienna nomogram	Biopsies should be directed more laterally (PZ). Repeat biopsies should be performed when initial biopsy shows no prostate cancer in total prostate volumes > 45 cc or TZ volumes > 25 cc	Based on patient's age and gland volume (8–18 cores)	- The combination of prostate size and patient age can help physicians in determining the most appropriate prostate biopsy sampling	- Disadvantages inherent to the transrectal route (see the main text).
Transperineal Route	Barzell	Grid-based biopsy using a biplanar TRUS probe, a brachytherapy stepper and a 0.5 mm brachytherapy grid. The prostate is divided in a proximal and distal halves by a transverse plane, each divided into four parts	24–48 (1–2 cores)	- “Dense” systematic sampling with excellent spatial localization (e.g., ideal in patients suitable for focal therapy)	- Can need for general anesthesia or intravenous sedation anesthesia. - Can be costly and time-consuming in performing both the procedure and histopathological analysis. - Can increase morbidity. - Risk of overdiagnosis of indolent cancers.
	Ginsburg	Twelve-sector template, two cores/sector. More number of cores for larger prostates	24–38, depending on the prostate volume	- Less cores than the Barzell scheme.	- Preferentially targets the PZ, carrying the risk of missing TZ or periurethral cancers.
	“Fan” pattern technique	Sampling of the right and left PZ in three sectors each: posterior medial, posterior lateral, anterior	12	- Can be used with the freehand biopsy technology.	- Can miss TZ tumors.
	Ten-sector systematic biopsy	Sampling of the right and left gland in five sectors each: anterior lateral, anterior medial, posterior lateral, posterior medial, lateral base	10	- Less morbidity because of the reduced number of cores.	- Can miss CZ tumors as this prostate zone is not sampled.

whether “cognitive” MRITB (C-MRITB) or software-assisted MRITB (properly said “fusion” MRITB [F-MRITB]) [8,11,64], as detailed in Table 4. Of note, each MRITB type can be performed with either the TRR or TPR, usually as outpatient procedures. While it is usually assumed that IB-MRITB provides the most precise targeting [65], there is currently no clear evidence proving the superiority of any targeting technique over the other in terms of cancer detection rate. Only a minority of works [66–67] found a clear superiority of F-MRITB versus C-MRITB. On the contrary, the FUTURE study [68], which is currently the only multicenter randomized controlled trial comparing all the three targeting techniques in men with previous negative biopsy, found no significant differences ($p > 0.9$) in the detection rate of csPCa between IB-MRITB (33%), C-MRITB (33%) and F-MRITB (34%). Despite being admittedly underpowered, those results have been confirmed in other relevant studies as summarized in Table 5 [68–75]. In a meta-analysis by Watts et al. [76] F-MRITB showed a non-significant trend towards improved cancer detection rate compared to C-MRITB (OR 1.13, $p = 0.32$), while in a meta-analysis by Bass et al. [77] the Authors found non-significantly different ($p = 0.55$) cancer detection rate between IB-MRITB (0.87), C-MRITB (0.81) and F-MRITB (0.81).

Overall, F-MRITB is gaining ever-increasing popularity as the reference standard for MRI-i-PB, as testified by the fact it is currently recommended over C-MRITB by the American Urological Association (AUA) and the Society of Abdominal Radiology (SAR) where resources, expertise and facility are available [78]. Differently from C-MRITB, F-MRITB combines targeting accuracy while avoiding costs and time-consumption currently related to IB-MRITB [64]. There are several commercially available platforms for F-MRITB, differing in image acquisition, software design and image tracking mechanisms (e.g., electromagnetic tracking or organ-based image registration), as well as facilities and probe configuration (endfire/sidefire) for using the TRR or TPR (Fig. 4). An overview of these systems and procedural steps exceeds the scopes of our review and can be found elsewhere [64,79]. Each system shows its own advantages and disadvantages potentially affecting the quality of the targeting process [64]. While some systems offer additional facilities such as the possibility to track and record biopsy sites to make re-sampling feasible in repeated biopsy sessions (e.g.,

during active surveillance), there are currently no platforms offering clear diagnostic superiority [64,80].

Among the technical factors inherent to F-MRITB, special emphasis should be given to the type of image registration as a potential major determinant of MRI-i-PB quality and accuracy [11]. Under this perspective, commercially available systems can be broadly grouped into those performing “rigid” or “elastic” (non-rigid) image registration (fusion). During rigid fusion, MRI images are intraoperatively overlaid onto TRUS images using anatomical landmarks, without adjustments for patient movement or prostate deformation occurring in real-time. On the contrary, elastic fusion accounts for this by fusing the 3D contours of both MRI and TRUS images and then correcting for deformation and movement using elastic deformation algorithms [64,81]. Basically, while rigid systems compensate for the rotational and translational differences in gland orientation, non-rigid methods also adjust image fusion by accounting for geometrical differences between MRI and TRUS prostate volumes [79]. Although non-rigid registration has been advocated as the method with greater potential for increasing targeting precision, and in turn diagnostic accuracy for csPCa, no differences have been found to date [82–83]. According to a meta-analysis by Venderink et al. [83] the odds ratio for the detection of csPCa was 1.45 (95% - confidence intervals: 1.21–1.73) versus 1.40 (95% confidence intervals 1.13 – 1.75) for non-rigid versus rigid registration, respectively.

From a quality-centered viewpoint, it is still difficult to define QA references in this setting, and standardized strategies to minimize the risk of misregistration and targeting margin error which affect the current systems [64]. Margin for registration error and related TRUS-MRI misalignment is supposed to be around 2–3 mm, and can depend on a variety of factors such as gland deformation induced by the TRUS probe or different bladder filling between MRI and TRUS [84]. In a post-hoc analysis of the Trio study cohort on 41 patients, Williams et al. [84] found that targeting error was the most common cause of failed MRI-targeted biopsy, explaining why adding systematic biopsy and/or *peri-target* biopsies is still advocated as a “safety net” against false-negative results of MRI-i-PB [11,32]. Additionally, there is some uncertainty on how to sample MRI targets. While some systems and operators minimize the ROI to the central zone of the most suspicious part of the target

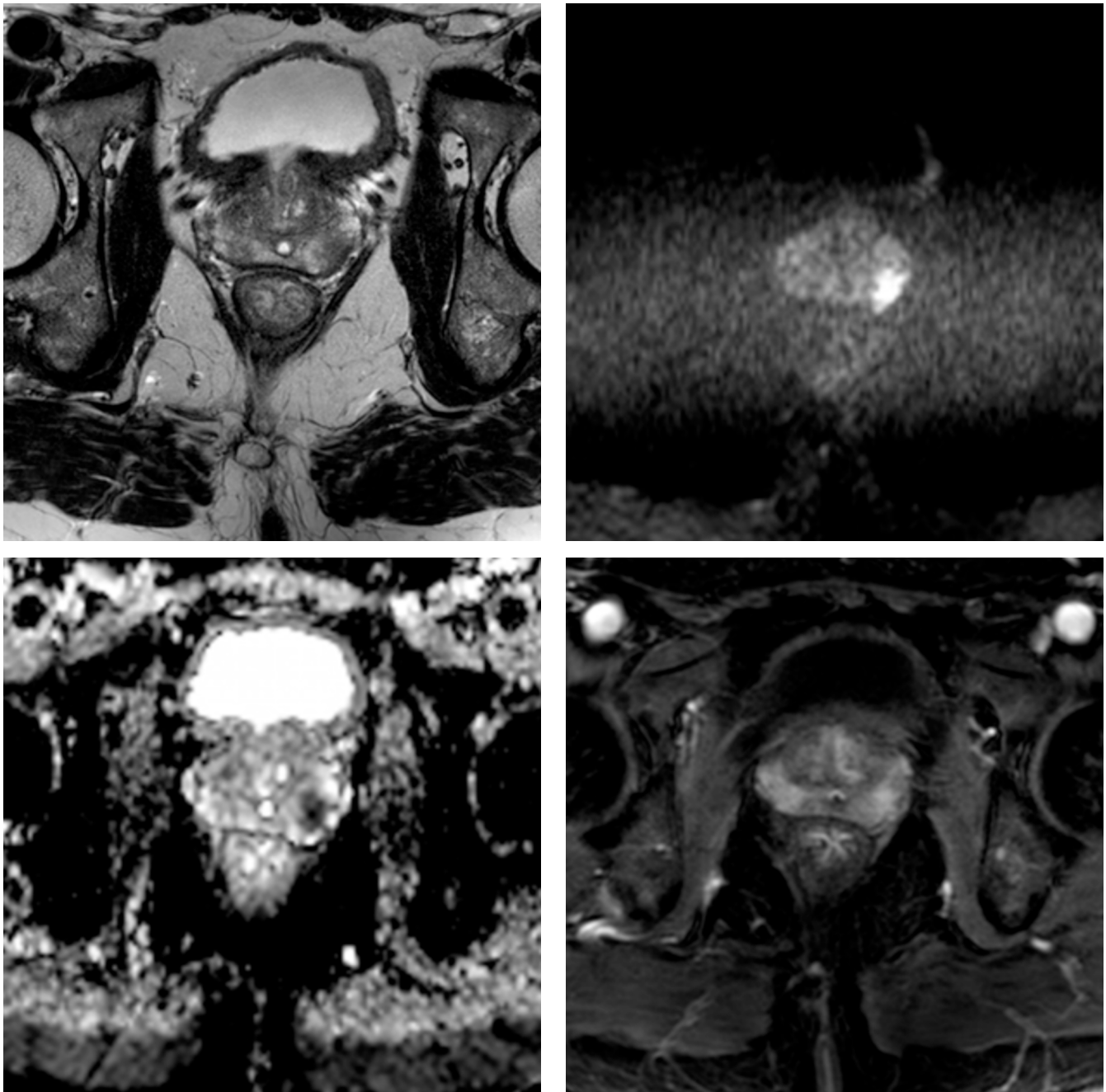


Fig. 3. Case of a 66 year-old biopsy-naïve patient who underwent prostate magnetic resonance imaging for raised prostatic specific antigen level (5.73 ng/mL) and suspicious digital rectal examination. Prostate MRI showed a 13 mm PI-RADS 4 lesion in the left basal peripheral zone, characterized by hypointensity on axial T2-weighted images (a), restricted diffusion with hyperintensity on the high b-value image (b) and hypointensity on the apparent diffusion coefficient map (c). No corresponding focal enhancement was observed (d). The patient underwent transperineal biopsy with targeted biopsies and transperineal biopsy according to the Ginsburg scheme (e). Targeted cores showed a Gleason score 4 + 3 disease.

aiming at sampling the most biologically relevant/aggressive portion of the tumor, other systems outline and sample the whole lesion to minimize undersampling and refine patient's risk with information on volume [64].

In the absence of guidelines, we assume that QC procedures for checking quality in this setting should consist of phantom calibration studies as per vendor instructions and regular audits on cancer detection rate and complications rate. Concerning the sampling technique, it is reasonable to assume that F-MRITB should be preferred wherever available as it provides a more objective and reproducible method to

target biopsies compared to C-MRITB while being much more easily implementable and feasible than IB-MRITB.

3.3. Operator's experience

Prostate biopsy is an operator-dependent procedure, requiring dedicated training. It is unclear how many biopsies should constitute the "learning-curve" phase, as literature reports numbers spanning from 100 to 1,500 [85–86]. However, adequate expertise and training have been advocated as a more relevant factor in determining the MRI-i-PB success

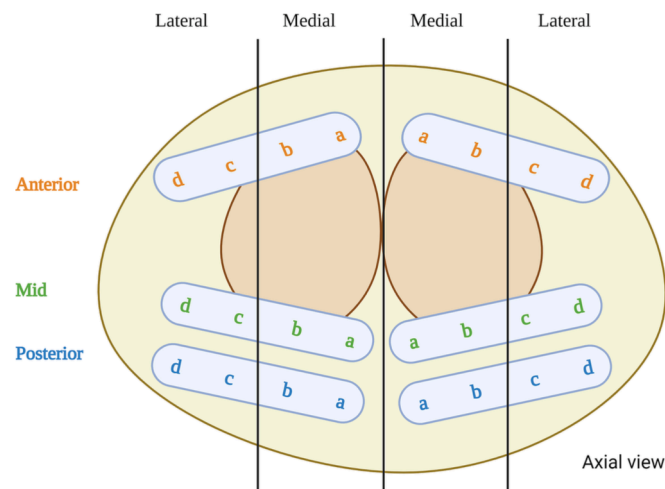


Fig. 3. (continued).

than the biopsy route or targeting technology per se [64]. In a study on 244 patients who underwent 1.5 T MRI, Stabile et al. [71] found that the operator's expertise was an independent predictor of cSPCa detection in targeted samples (OR 1.7), especially when using F-MRITB (OR 1.9). To date, no definite recommendations establish QA references in this setting. It has been argued that less experienced operators should acquire a larger number of targeted cores (e.g., 4–5) compared to experienced operators in order to minimize the risk of targeting errors [87].

First procedural steps requiring experience are those related to prostate and lesion segmentation on MRI images, TRUS acquisition and segmentation, and MRI-TRUS image co-registration in F-MRITB [79]. Regardless of the targeting technique, the operator should be able to outline the ROI if previously undone [8]. Additionally, aligning MRI and TRUS images implies the well-trained capability of identifying the zonal anatomy of the prostate and anatomical landmarks favoring the required cognitive adjustments [64]. The latter should account for subtle position shifts of the prostate occurring when prostate biopsy is performed in a different patient position compared to supine MRI, as typical when using the TRR [88].

Experience is crucial even in the subsequent step of delivering targeted biopsies. In the ideal setting in which there is close relationship within the reporting radiologists, and lesions are clearly outlined in a reporting template, the operator, if not an imaging-specialist, should be able to correctly interpret reported information or interact with the radiologist using common interpretative rules such as the PI-RADS guidelines. This can be useful when, for example, PZ target lesions are less conspicuous or evident on transverse T2-weighted images, which are most often used for prostate and target contouring given the high anatomical content, although it is still unclear which MRI sequence performs better for fusion purposes in terms of cancer detection rate. Depending on the fusion-software and operator's knowledge of the PI-RADS scoring system, different MRI sequences can be chosen, for example diffusion-weighted imaging (DWI) [64]. It has also been shown that adding one more fusion plane to the transverse acquisition improves the cancer detection rate [89].

The operator should also be familiar with the Prostate Imaging Quality (PI-QUAL) score to appreciate whether reference images for guiding the procedure are affected by relevant artifacts, and in general predict how much useful a certain MRI examination can be to obtain acceptable co-registration and targeted sampling. Additional awareness of MRI technical factors can be useful, e.g., adjusting lesion localization in the prostate according to the orientation of the transverse plane, as the topography of the “apex”, “mid-gland” and “base” levels can subtly differ when the transverse plane is perpendicular to the long axis of the prostate or, alternatively, the posterior prostate wall. Of note, the latter

plane is assumed to better match the position of the transrectal probe [8]. Even under this optimal technical condition, the operator should be able to adjust biopsies for the variability inherent to the localization of lesion level on MRI reports, which depends on the absence of well-defined anatomical landmarks to separate them. Greer et al. [90] found 61% inter-agreement only in reporting the exact level of lesions location (apex, mid-gland or base) on the PI-RADS version 2 sector map, suggesting that this can lead to inaccuracies in guiding biopsies. All the above factors are even more relevant when C-MRITB is performed instead of F-MRITB.

3.4. Role of image quality

The PI-QUAL score has been recently introduced as a standardized system to assess prostate MRI image quality [91]. In a multireader study on 247 patients by Karanasios et al. [92], radiologists assessed an MRI examination as suitable for guiding a fusion biopsy depending on image quality as assessed by this new score. Only 60% of scans scored PI-QUAL 1 or 2 were judged as suitable for this task, whereas the percentage increased to 94% and 100% in the case of examinations scored PI-QUAL 3 and PI-QUAL 4–5, respectively. The same Authors found that higher PI-QUAL scores led to an increased likelihood of assessing MRI as negative (from 50% for PI-QUAL 3 to 87% for PI-QUAL 5), and a decreased number of indeterminate PI-RADS 3 assignments (from 31.8% for PI-QUAL 3 to 10.4% for PI-QUAL 5), suggesting that image quality is of pivotal importance in determining biopsy decisions, as well as avoiding unnecessary procedures.

One might argue that easy-to-detect larger PI-RADS 4–5 lesions can be diagnosed even in a low-quality PI-QUAL 2 examination, thus impairing MRI-i-PB only at a limited extent [7]. This assumption is apparently supported by a study including 46 patients [93] in which per-region sensitivity and specificity for cSPCa were comparable between PI-QUAL ≤ 3 and PI-QUAL > 3 scans. However, the study also showed a significantly lower positive predictive value (36.2% versus 56.1%; $p = 0.001$) and cancer prevalence (16.7% versus 30.2%; $p = 0.008$) in PI-QUAL ≤ 3 versus PI-QUAL > 3 examinations, suggesting that, while additional factors can contribute to the diagnostic accuracy of the MRI-i-PB compared to image quality alone, the latter reduces the risk of false-positive MRI results and unnecessary biopsies. This is in accordance with other results showing that the main impact of improved image quality is on readers' confidence in ruling-out rather than ruling-in suspicious findings (10%, 67% and 100% for PI-QUAL 3, 4 and 5 scans, respectively) [92].

Overall, we believe that, while still evolving, the PI-QUAL will be central in any QC process assessing image quality [8]. The system can

Table 4

Currently available techniques for targeting suspicious prostate regions of interest (ROIs) outlined on magnetic resonance imaging (MRI). TRUS = transrectal ultrasound.

MRI target biopsy (MRITB) approach	Real-time imaging guiding biopsy acquisition	Strategy for identifying biopsy targets	Advantages	Disadvantages
In-bore MRITB	MRI with the patient placed prone, head-first and with a rectally inserted needle guide.	Direct image confirmation of needle deployment within the target.	- Useful for small and difficult to reach lesions.	- High implementation costs. - Time-consuming procedure (up to 60 min). - Concurrent systematic sampling cannot be performed.
Cognitive fusion MRITB	TRUS	The operator identifies and localizes biopsy target(s) on TRUS images by subjectively/visually overlapping suspicious ROIs analyzed on separately presented MRI images.	- No need for expensive registration systems. - Fast and cheap approach for sampling larger lesions. - Combination with concurrent systematic sampling.	- Need for experienced readers capable to assess normal anatomy and suspicious findings on both TRUS and MRI images, having in mind the 3D configuration of the prostate. - Challenging for anterior and basal lesions. - No confirmation of biopsied areas against MRI, preventing precise anatomical localization and focal therapy.
Software-assisted fusion MRITB	TRUS with dedicated software registering MRI images over real time ultrasound images to create a 3D prostate model.	Previously defined MRI ROIs are fused with real time imaging, thus allowing precise targeting	- Preserved targeting accuracy. - Combination with concurrent systematic biopsy. - Accurate in detecting smaller lesions - Accurate in making diagnoses other than cancer (e.g., prostatitis)	- Equipment costs. - Margin errors in image co-registration.

Table 5

Overview of relevant studies comparing different targeting techniques for prostate biopsy, namely in-bore magnetic resonance (MRI) targeted biopsy (IB-MRITB), cognitive MRI targeted biopsy (C-MRITB) and fusion MRI targeted biopsy (F-MRITB). CDR = cancer detection rate; csPCa = clinically significant prostate cancer.

Study design	Targeting techniques under comparison	Main results
<i>Wysok et al., 2014 (PROFUS trial) [69]</i>	125 men with 172 MRI targets/ROIs undergoing F-MRITB (first urologist) followed by C-MRITB and systematic biopsy (second urologist)	C-MRITB versus F-MRITB - F-MRITB provided non-significant increase in CDR of csPCa compared to C-MRITB (20.3% versus 15.1%; $p = 0.0523$) - F-MRITB more accurate for smaller cancers - F-MRITB more useful in providing histological diagnoses other than cancer (e.g., prostatitis)
<i>Lee et al. 2016 [70]</i>	296 men (prior positive biopsy, biopsy naïve, prior negative biopsy).	C-MRITB versus F-MRITB Non-significant difference in the detection of high-grade cancer (-1.4%; $p = 0.6$). However, the performance of each technique varied in specific biopsy locations, and the outcomes of both techniques were complementary, so that combination is recommended
<i>Wegelin et al., 2018 (FUTURE trial) [68]</i>	234 of 665 men with prior negative biopsy randomized to IB-MRITB, C-MRITB and F-MRITB	IB-MRITB versus C-MRITB versus F-MRITB Non-significant ($p > 0.9$) differences in CDR of csPCa (33% for IB-MRITB, 33% for C-MRITB and 34% for F-MRITB)
<i>Simmons et al., 2018 (PICTURE trial) [72]</i>	Prospective inclusion of 249 patients (prior biopsy)	C-MRITB versus F-MRITB CDR 31.3% for F-MRITB versus 28.4% for C-MRITB
<i>Cornud et al. 2018 [73]</i>	88 men (47 biopsy-naïve, 41 prior negative biopsy)	C-MRITB versus F-MRITB - CDR 90.9% for F-MRITB versus 70.5% for C-MRITB - More fusion cores than cognitive cores were on target (76.2% vs 42.0%).
<i>Stabile et al. 2018 [71]</i>	244 men who underwent C-MRITB and F-MRITB during the same session by three still inexperienced readers.	C-MRITB versus F-MRITB CDR 58% for F-MRITB versus 45% for C-MRITB
<i>Hamid et al. 2019 (SmartTarget trial) [75]</i>	129 men with prior negative or positive TRR biopsy randomized to one of two different arms of TPR biopsy with up to 3 per-target cores: (i) C-MRITB first followed by F-MRITB performed by a second different operator; (ii) F-MRITB first followed by C-MRITB performed by a second different operator.	C-MRITB versus F-MRITB Comparable CDR of csPCa in 93/129 men (86%). Each technique identified 13 cases missed by the other, suggesting that both techniques should be used together.
<i>Elkhoury et al., 2019 (PAIREDCAP trial) [74]</i>	248 biopsy-naïve men received same-session systematic biopsy followed by C-MRITB and then F-MRITB. Fifty-two men with negative MRI undergoing systematic biopsy alone served as a control group (15% CDR).	C-MRITB versus F-MRITB CDR of 47% for C-MRITB, 60% for systematic biopsy or either F-MRITB, and 70% when combining systematic and targeted biopsy.

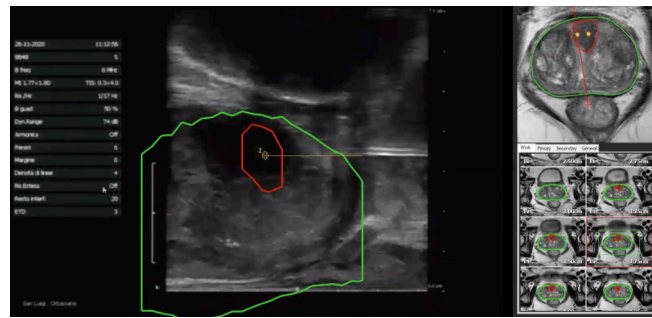


Fig. 4. Software assisted “fusion” biopsy obtained by co-registering the volume of magnetic resonance images with real-time transrectal ultrasound (green contour) to sample the region of interest (red contour) corresponding to the suspicious magnetic resonance imaging finding (a). The procedure was performed with a transperineal approach with the patient lying in the lithotomy position (b).

also serve in QA programs to quantify how much image quality can affect the diagnostic yield of MRI-i-PB, as commented above. As far as we know, no previous studies investigated whether PI-QUAL categorization affects the diagnostic yield of MRI-i-PB when using different sampling techniques (e.g., F-MRITB versus C-MRITB). We believe this is of importance, as one can hypothesize that, while software-assisted fusion biopsy is the most robust standard available, C-MRITB can act as a safety-net technique when poor image quality prevents from using F-MRITB (e.g., because of prostate displacement or deformation from rectal content).

4. Future directions

It has been argued that, while the MRI-i-PB diagnostic pathway is of benefit, targeted biopsies can result into many patients to be diagnosed and treated to avoid just one csPCa-related death [94]. In this light, topics for further research in the attempt of stratifying indications to

MRI-i-PB and enhance its value further in clinical practice include adjustment of biopsy decisions and schemes according to clinical information (e.g., PSAD and/or additional data), biopsy thresholds (e.g., PI-RADS 4 instead of 3, or patient risk), strategies for facing the possible phenomenon of histologic grade shifts of targeted biopsy cores (e.g., by using a higher grade for clinical significance or adjusting the histologic evaluation), and treatment choices [94–95]. There is increasing interest in driving individualized “precision” MRI-i-PBs based on clinical risk assessment, and even relevant MRI findings for driving accurate biopsy (e.g., lesion size and location). However, it should be kept in mind that the main purpose of MRI-i-PB is not only making reliable diagnosis of PCa, but rather providing information for choosing the best therapeutic approach in each patient [96]. Whether molecular imaging using positron emission tomography (PET)/ computer tomography (CT) or PET/ MRI can contribute to this task in the primary diagnosis is an ongoing matter of debate, as detailed elsewhere [11].

Other advances relate to F-MRITB technique, for example in

improving targeting precision with automatic segmentation and deformable co-registration with real-time motion correction [64]. A different line of research focuses on optimizing ultrasound, for example using ultra-high frequency probes for better anatomical definition (micro-ultrasonography) or a multiparametric technique (e.g., combination of B-mode with elastography and/or contrast enhanced ultrasound) for better biopsy guidance or even as a diagnostic alternative to MRI [11,64]. Considering the biopsy delivering technique, robotic-assisted prostate biopsy is the next frontier under investigation, with promising initial results, though large-scale validation against non-robotic-assisted biopsy is still lacking [97–98].

5. Conclusions

MRI-i-PB has become central in the current diagnostic pathway of csPCa, highlighting the need for a multidisciplinary “quality chain” taking care of its different steps and adherence to the presented QA and QC benchmarks. As far as biopsy is concerned, there is still room for improvement in refining the MRI or combined clinical-MRI threshold for triggering prostate biopsy, and schemes for performing targeted biopsy. While focal saturation sampling is gaining popularity, there is currently no standardized template that can be offered as a stand-alone alternative to the combination of targeted and systematic biopsy.

Biopsy acquisition represents an evolving scenario, as the TPR is currently recommended as a better option than TRR. Regardless, of the biopsy route, F-MRITB is increasingly used as a safe and less costly alternative to IB-MRITB, though there is no definitive proof it performs better than C-MRITB. On the other hand, the true pre-requisites for a reliable diagnostic pathway are image quality (to avoid unnecessary biopsies) and the operator’s experience, which should include a multidisciplinary approach.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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