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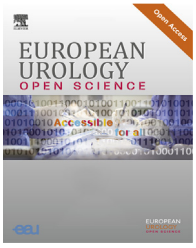

European Association of Urology

Review – Prostate Cancer

Enhancing Prostate Cancer Detection Accuracy in Magnetic Resonance Imaging–targeted Prostate Biopsy: Optimizing the Number of Cores Taken

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Abstract

Background and objective: The shift toward targeted biopsy (TBx) aims at enhancing prostate cancer (PCa) detection while reducing overdiagnosis of clinically insignificant disease. Despite the improved ability of TBx in identifying clinically significant PCa (csPCa), the optimal number and location of targeted cores remain unclear. This review aims to assess the optimal number of prostate biopsy magnetic resonance imaging (MRI)-targeted cores to detect csPCa.

Methods: A narrative literature search was conducted using PubMed, focusing on studies published between January 2014 and January 2024, addressing factors influencing targeted core numbers during prostate biopsy. The search included both retrospective and prospective studies, prioritizing those with substantial sample sizes and employing terms such as "prostate biopsy", "mpMRI", "core number", and "cancer detection".

Key findings and limitations: Two biopsy cores identified csPCa in 55–65% of cases. This detection rate improved to approximately 90% when the number of cores was $\geq$5. The inclusion of perilesional and systematic biopsies could maximize the detection of csPCa (from 10% to 45%), especially in patients under active surveillance or with prior negative biopsy results, although there is an increase in the overdiagnosis of indolent tumors (from 4% to 20%). Transperineal software-assisted target prostate biopsy may enhance cancer detection,

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particularly for tumors located at the apex/anterior part of the prostate. Increasing the number of TBx cores may incrementally raise the risk of complications (by 2–14% with each added core) and result in severe pain and significant discomfort for up to 17% and 25% of TBx patients, respectively. However, the overall rate and severity of these complications remain within acceptable limits.

Conclusions and clinical implications: The optimal number of cores for targeted prostate biopsies should balance minimizing sampling errors with effective cancer detection and should be tailored to each patient's unique prostate characteristics. Up to five cores per MRI target may be considered to enhance the detection of csPCa, with adjustments based on factors such as prostate and lesion volume, Prostate Imaging Reporting and Data System, biopsy techniques, complications, patient discomfort, and anxiety.

Patient summary: In this report, we found that increasing the number of biopsy cores up to $\geq$5 improves the detection rates of significant prostate cancer significantly to around 90%. Although inclusion of nearby and systematic biopsies enhances detection, increasing the biopsy count may lead to higher risks of complications and indolent tumors. A customized biopsy approach based on multiple variables could be helpful in determining the appropriate number of targeted biopsies on a case-by-case basis.

1. Introduction

Prostate cancer (PCa) detection has seen a paradigm shift over the past few years with the introduction of multiparametric magnetic resonance imaging (mpMRI)-guided biopsy [1]. The use of mpMRI as a triage test in men with elevated prostate-specific antigen levels and a suspicion of PCa and, consequently, the shift toward targeted biopsy (TBx) resulted not only in improved detection of clinically significant PCa (csPCa), but also in decreased rates of insignificant PCa diagnosed. This, in turn, has a positive impact in minimizing the risk of overtreatment and treatment-related complications, optimizing resource utilization and reducing postbiopsy complications through a reduction in the overall number of biopsies performed [2]. Proper biopsy planning, which includes determining the optimal number of targeted cores and biopsy acquisition techniques (namely, biopsy route and technique), is a key process in the PCa diagnostic pathway. Despite this, a significant knowledge gap persists in determining the optimal number and location of targeted cores within a region of interest (ROI) [3]. Furthermore, the lack of consensus regarding the optimal sampling technique during TBx underscores the necessity for defining standardized protocols.

This review addresses the multifaceted aspects that influence the number of targeted cores during prostate biopsy, with a focus on optimizing the balance between csPCa and insignificant cancer detection. Various factors are explored, including prostate characteristics, patient demographics, biopsy techniques, and magnetic resonance imaging (MRI) quality. By investigating the impact of these factors, we aim to provide valuable insights for improving the accuracy and efficiency of MRI-guided prostate biopsies.

2. Methods

A literature search was conducted using PubMed to identify relevant studies published between January 2014 and January 2024. We focused the literature search on studies that addressed factors influencing the optimal number of targeted cores to detect csPCa during prostate biopsy. Both retrospective and prospective studies were considered. The selection process prioritized level 1 studies with adequate sample sizes. The MeSH search terms included "prostate biopsy", "mpMRI", "core number", "cancer detection", and "MRI-targeted". The collected studies formed the basis for a narrative analysis of the literature, which was conducted based on the relevance of each publication and consensus among authors.

3. Results

3.1. Assessing the optimal number of MRI-targeted cores

Table 1 includes studies focused on optimizing the quantity of biopsy cores obtained from each MRI-identified target during focal saturation biopsies. Our literature review identified one randomized controlled trial [4] that assessed the detection rates of csPCa for conventional transperineal (TP) MRI/transrectal ultrasound (TRUS) fusion biopsy (TBx) compared with target saturation biopsy (TSx) in 170 men. Participants were divided equally, with 85 men randomized to receive conventional TBx using four cores per lesion and the other 85 assigned to TSx with nine cores per lesion. The study failed to show significant differences

Table 1 – Summary of studies focused on optimizing the quantity of biopsy cores obtained from each MRI-identified target during focal saturation biopsies

	Study design	No. of patients	Patient type	Number of targeted cores under analysis	Biopsy technique	Type of systematic biopsy	Biopsy approach	Main results
Saner et al [4]	Prospective randomized trial	170	118 biopsy naïve, 52 had ≤3 negative TRUS biopsies	randomized to conventional target biopsy with 4 cores (n = 85) versus target saturation with 9 cores (n = 85)	MRI/TRUS fusion	Extended SBx with 24 cores	TP	No significant difference in detection rates between TBx and TSx methods
Hansen et al [5]	Prospective study	487	25% no previous biopsy, 44% previous negative biopsy, 31% active surveillance	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-core biopsy	Software-assisted fusion MRI	All men had 24-core SBx	TP	1. 10–20-core focal saturation biopsy comparable with target + systematic biopsy (CDR 91%) 2. Four-core target biopsy can suffice for large, highly suspicious lesions (CDR 76%)
Tracy et al [6]	Prospective study	104	82% with prior biopsy)	5 cores/target lesion	Software-assisted fusion MRI	12-core SBx using the 12 computer-generated sectors as a guide	TR	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
Lu et al [7]	Retrospective	744	52% prior negative biopsy, 48% active surveillance	5 cores (interquartile range 3–5) from each ROI	Software-assisted fusion MRI	12-core SBx	NA	Five-core sampling missed substantially fewer cancers than two-core sampling
Zhang et al [8]	Retrospective	330	Active surveillance and prior negative biopsy	≥5 cores/lesion	Cognitive MRI-targeted TRUS	19 (6%) underwent SBx and TBx, and 311 (94%) underwent only targeted biopsies Type of SBx not reported	TR	1. 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 2. Target yield for 5 cores was 35%
Ploussard et al [10]	Retrospective	478	Biopsy naïve (repeat biopsy and active surveillance excluded	<2 versus ≥5	Software-assisted fusion MRI	Not clearly reported, as a retrospective study, probably data not shown	TR	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
Tschirdewahn et al [11]	Retrospective	213	132 biopsy naïve, 81 with previous negative biopsy	Median of 4 cores for target biopsy, 9 cores for target saturation, and 24 cores for systematic biopsy	MRI/TRUS-fusion biopsies (target biopsy and target saturation) compared with extended systematic biopsies	24 SBx cores	TP	The CDR was greater for target saturation (99%) than for target biopsy (87%) and systematic biopsy (82%)
Lahoud et al [14]	Retrospective	254	Biopsy naïve	Median of 5 cores per target	MRI-ultrasound fusion or cognitive registration using a brachytherapy grid, and targeted and perilesional biopsies	Not reported	TP	1. For PI-RADS 4 and 5 lesions, perilesional biopsy in addition to targeted biopsy detected 9% more csPCa cases, at the cost of an increased 4% overdiagnosis of ciPCa. 2. For PI-RADS 3 lesions, perilesional biopsies did not increase the CDR for csPCa
Beetz et al [9]	Retrospective	451	NA	≥3 cores per target	MRI/TRUS fusion. Targeted tissue samples were taken from central and peripheral parts within the index lesion (no penumbra)	All patients underwent 10-core SBx	NA	There is a progressive increase in detection rates with an increasing number of biopsy cores: 73% with one core, 88% with two cores, 97% with three cores, and approximately 100% with four cores

CDR = cancer detection rate; ciPCa = clinically insignificant prostate cancer; csPCa = clinically significant prostate cancer; MRI = magnetic resonance imaging; NA = not available; PI-RADS = Prostate Imaging Reporting and Data System; ROI = region of interest; SBx = systematic biopsy; TBx = targeted biopsy; TP = transperineal; TR = transrectal; TRUS = transrectal ultrasound; TSx = target saturation biopsy.

in the detection rates of csPCa between the four- and nine-core TBx strategies (100% vs 92%; $p = 0.058$). Nonetheless, the presence of an imbalanced csPCa prevalence distribution among the participants and the possibility of insufficient statistical power to detect a difference may have affected these findings.

Hansen et al [5] performed a prospective study evaluating the PCa detection rates of various TP-MRI-TBx templates between the Ginsburg scheme and potential modifications. The outcome of interest was represented by the detection of grading group (GG) ≥2 PCa, which was compared between two-core TBx, extended TBx (eTBx; TBx plus two systematic cores in target sector, four cores in total), saturation TBx (sTBx; two cores from the target plus two cores from the target sector plus two cores from each of the adjacent sectors), and ipsilateral TBx (iTBx; TB plus ipsilateral biopsy of 12 systematic sector cores, 14 cores in total) to combined TBx + systematic biopsy (SBx; standard TBx plus 18–24 systematic sector cores, 20–26 cores in total). The detection of GG ≥2 PCa increased with increasing systematic core number: two-core TBx detected only 67% of the cancers, eTBx detected only 76% (four cores), while sTBx (10–20 core) and iTBx (14 cores) both detected >90% of the diseases. The authors concluded that sTBx detected GG 2–5 cancer in 25% more men than a two-core TBx approach, and in almost as many men (91%) as the 20–26-core combined TBx + SBx, while needing only ten to 20 cores.

Tracy et al [6] prospectively enrolled 104 patients to investigate the incremental diagnostic value of each additional TBx core. In this study, five biopsy cores were collected and examined individually from each Prostate Imaging Reporting and Data System (PI-RADS) ≥3 lesion. The detection of csPCa increased incrementally with each additional biopsy core among men with lesions rated higher than PI-RADS 3. Specifically, the detection rates rose from 26% with the first core to 44% with the third core, and reached 52% with the fifth core. In contrast, for lesions rated as PI-RADS 3, detection rates increased from 1% with the first core to 4% with the third core, and finally to 9% with the fifth core. Furthermore, men with lesions rated higher than PI-RADS 3 exhibited a greater likelihood of pathological upgrading with each additional TBx, especially to GG ≥2. Interestingly, GG 1 detection seems not to increase when more cores were taken.

Lu et al [7] conducted a retrospective study where multiple TBx cores were performed from each suspicious area, followed by a 12-core SBx. In a separate group, lesions were targeted using a predefined five-core template. The study included 744 patients with 581 lesions diagnosed with PCa. Notably, 77% of GG 2 tumors and 72% of GG >2 tumors were identified with a two-core sampling approach. However, this method missed 16% of csPCa cases on the first biopsy, 27% in patients with prior negative results, and 32% in those under active surveillance (AS). The authors concluded that a limited two-core targeted sampling strategy detects the majority of csPCa cases but misses nearly a quarter of cancers compared with a more comprehensive five-core approach.

Similarly, Zhang et al [8] evaluated retrospectively 330 patients with a cognitive MRI-TBx transrectal (TR) biopsy. Each lesion was targeted with at least five sequentially labeled core samples. The yield for detecting csPCa was found to be 26% (87 out of 330) with one core, 33% (108 out of 330) with three cores, and 35% (116 out of 330) with five cores.

By increasing the number of biopsy core samples from one to three per target, and then from three to five per target, the detection rate of csPCa improved by 6.4% (21 out of 330) and 2.4% (eight out of 330), respectively. Therefore, the yield for csPCa detection was 26% with one core, 33% with three cores, and 35% with five cores.

In a retrospective analysis, Beetz et al [9] evaluated 451 patients to determine the optimal number of MRI-targeted prostate biopsy cores required for the most accurate histopathological diagnosis of the index lesion. This study involved both a ten-core systematic prostate biopsy and an MRI TBx, which included sampling of at least three cores from the index lesion. The sequence of core sampling was recorded meticulously throughout the study. The initial biopsy core yielded the most relevant histopathological diagnosis in 331 cases (73%), the second core in 66 cases (15%), the third core in 39 cases (9%), the fourth core in 13 cases (3%), and the fifth core in two cases (<1%).

In a retrospective study focusing on radical prostatectomy, Ploussard et al [10] analyzed the data from 478 patients and observed a significant continuous decrease in the rate of pathological upgrading as the number of TBx cores per lesion increased. Specifically, the upgrading rate declined from 56% to 26% when fewer than two, or five or more TBx cores were obtained ($p < 0.01$). The study determined that the minimum numbers of TBx cores per lesion required to reduce the risk of upgrading to approximately 30% were 4 for PI-RADS 3 lesions and 3 for PI-RADS 4–5 lesions. Intriguingly, while increasing the number of cores tends to reduce the rate of upgrading, it conversely leads to a higher incidence of downgrading, suggesting a delicate balance in the number of cores taken to achieve an accurate histological assessment.

Tschirdewahn et al [11] conducted a study with 213 patients to evaluate the effectiveness of detecting csPCa using MRI-TBx (TBx, median of four targeted cores per lesion) and TSx, and combined the targeted cores from the lesion with additional cores from the adjacent SBx sectors, resulting in a total of nine to ten TSx cores)—compared with extended SBx (24 systematic cores). These biopsies were performed during grid-directed TP sector biopsies under general anesthesia. Of note, TSx had a remarkably high detection rate for csPCa (99%), significantly higher than both SBx (81%) and TBx (89%). SBx detected significantly more of the 72 low-risk PCa lesions than TBx (99% vs 68%, $p < 0.001$) and 10% ($p = 0.1$) more than that detected by TSx. Increasing evidence indicates that an effective approach involves concentrating the biopsy cores near the MRI lesion [12], known as "focal saturation biopsy". This entails extracting three to five cores from the ROI and the surrounding "penumbra", even without a direct MRI correlate [13]. In a retrospective study using cognitive registra-

tion brachytherapy grid, Lahoud et al [14] evaluated the impact of adding extra prostate core biopsies around the perimeter of the target lesion—referred to as the penumbra, approximately 5 mm from the lesion—on the effectiveness of TBx. A median of five TBx and five perilesional biopsy (PLB) cores were taken, depending on the target size. For PI-RADS 4 and 5 lesions, combining PLBs with TBx detects an additional 9% of csPCa cases, but also results in a 4% increase in the detection of indolent PCa. However, for PI-RADS 3 lesions, PLBs do not improve the detection rate of csPCa. Other recent studies support this strategy, revealing that SBx on the same side of a negative targeted ROI frequently detects csPCa [15]. For example, Brisbane et al [12] showed that 90% of csPCa cores are located within a 10-mm radius from the surface of the ROI. However, only 65% of these cores are within the ROI itself. This suggests that a significant portion of csPCa cores can be found in the immediate vicinity outside of the initially identified area. Furthermore, higher MRI grades correlate with a higher percentage of csPCa cores found within the ROI, with the specific percentages being 50% for grade 3, 60% for grade 4, and 74% for grade 5.

Although PLB increased the detection rate of csPCa compared with TBx alone, the combination of these approaches missed approximately 30% of the csPCa cases identified with additional random biopsy cores, notably including a significant 15% of cases located contralaterally to the index tumor [16]. The largest scheme, including three TBx and 24 SBx cores, identified a small but statistically significant 4% increase in the detection rate of csPCa compared with the second-largest scheme. TBx alone identified only 62% of the csPCa cases. These results increased to 72% by adding four PLB cores and to 91% by adding 14 SBx cores [16]. In an AS protocol for low-risk or very-low-risk PCa patients, Novara et al [16] evaluated the improvement in diagnostic accuracy through perilesional and various biopsy schemes during TBx. Data from 112 consecutive patients with positive mpMRI undergoing biopsy were collected. The interventions included TR TBx, involving three-core TBx and concurrent TR 24-core SBx. The diagnostic yield of different biopsy schemes (TBx only, TBx + four PLB cores, TB + 12-core SBx, and TB + 24-core SBx) was assessed. Results showed that the detection rate of higher-grade cancers (GG $\geq$2) increased to 30%, 39%, and 49% by adding four PLB, 14 SBx, and 24 SBx cores, respectively, to TBx cores. However, the combination of PLB and TBx cores missed a substantial percentage of csPCa cases identified by more SBx cores, including some diagnosed by the combination of TBx plus 24-core SBx only. This was at the cost of an increasing diagnosis of non-CS cancers, rising from 10% with TBx only to 16% and 19% by adding four PLB cores and 14 RB cores, respectively.

The study concludes that PLB biopsy enhances the detection rate of higher-grade cancers compared with TBx alone but emphasizes the importance of including more SBx cores in identifying csPCa, especially in lesions with a PI-RADS score of 4 in AS patients.

These findings underscore the importance of countering the target accurately. This can significantly influence the number of cores taken from the "umbra" of the ROI (typically three to five cores based on lesion volume) and related penumbra [13].

In conclusion, the optimal core number can range from 3 to 5 for TBx in different scenarios. Improvement in the detection rates have been observed with the SBx and eTBx approaches, involving ten to 20 targeted cores or additional systematic cores, respectively, which notably enhance csPCa detection rates beyond 90%. Incorporating PLB alongside targeted cores further refines the detection accuracy, suggesting that a multifaceted approach is paramount. Specifically, a strategy deploying at least five targeted cores is recommended for lesions with a PI-RADS score of above 3, with adjustments based on prior biopsy outcomes and PI-RADS scores to tailor the approach effectively. This tailored strategy, integrating TBx, PLBs, and SBx, offers a balanced pathway to maximizing csPCa detection while considering procedural invasiveness.

3.2. *Additional factors that might influence the number of MRI-targeted cores*

3.2.1. *Biopsy techniques*

There is still uncertainty regarding how to sample MRI targets. Some systems and operators selectively narrow the ROI to the central zone of the most suspicious area in the target, aiming to sample the most biologically relevant and aggressive portion of the tumor. In contrast, alternative systems opt to outline and sample the entire lesion, mitigating the risk of undersampling and enhancing patient risk refinement through comprehensive volume information. Three primary techniques for MRI target biopsy are available, depending on the type of real-time imaging guiding the procedure and the integration of native MRI images with real-time imaging. These techniques include in-bore MRI-TBx (IB-MRI-TBx) and the fusion techniques, namely, "cognitive" MRI-TBx or software-assisted MRI-TBx, referred to as "fusion" MRI-TBx. While it is plausible that IB-MRI-TBx offers the most precise targeting [17], there is currently no definitive evidence establishing the superiority of any targeting technique in terms of cancer detection rate.

Assessing the optimal biopsy method is key, where a recent post hoc analysis of the TRIO study [18] found that a targeting error was the most common cause of failed MRI-TBx. Additionally, it is more practical and feasible than IB-MRI-TBx, where the inclusion of a few extra target cores might adversely affect the cost effectiveness of the procedure.

3.2.2. *Access route*

The efficacy of TR-TBx in enhancing the detection of csPCa remains uncertain. Some research indicates that TP biopsy could potentially increase the detection rates of PCa and csPCa [19], thereby aligning more closely with final pathology outcomes [20]. This advantage is particularly noted for lesions located in the transition/central, anterior, and apex regions of the prostate, where TP MRI-guided biopsy may surpass the TR method in effectiveness. Although a recent meta-analysis [21], primarily comprising retrospective studies, found no significant statistical difference in csPCa detection between the TR and TP approaches, it still identified a higher detection rate for csPCa in anterior (odds ratio

[OR] 2.17, 95% confidence interval [CI] 1.46–3.22; $p < 0.001$) and apical (OR 1.86, 95% CI 1.14–3.03; $p = 0.01$) lesions with the TP approach than with the TR approach. In a secondary analysis of the PREVENT trial [22], the detection rates of csPCa were comparable between the TP and TR approaches (53% TP vs 50% TR, adjusted difference 2.0%; 95% CI –6.0, 10). Despite these findings, the necessity for confirmation through prospective studies remains paramount.

3.2.3. *Prostate and lesion features*

Errors in targeting and issues in sampling may occur, even if an adequate number of cores have been taken. Factors that may contribute to these issues include prostate volume, volume lesion, and location.

The presence of a high prostate volume [18,23] due to benign prostatic hyperplasia might result in greater needle tip deflection, potentially making certain prostate areas challenging to access further reducing biopsy accuracy [24].

In smaller prostates (<45 ml), four-core eTBx detected 82% of the GG 3–5 cancers ($p = 0.039$).

Similarly, lesion volume might affect the ability to detect csPCa, where TBx and eTBx were less likely to detect GG $\geq$2 cancer in men with ROI <0.5 ml (TBx, 55%; eTBx, 69%) than in men with larger lesions (TBx, 76%; eTBx, 82%) [5].

Significant lesions missed with IB-MRI-TBx most often had involvement of dorsolateral (58%) and apical (37%) segments, and missed segments with TRUS biopsies were located anteriorly (79%), anterior mid-prostate (50%), and anterior apex (23%) [25].

3.2.4. *Number of lesions*

While mpMRI proves accurate in identifying the most suspicious lesion, its precision diminishes when detecting smaller PCa foci, particularly in cases of multifocal disease. The European Association of Urology guidelines recommend the combined use of SBx and TBx in the presence of positive mpMRI. However, the necessity for TBx of each suspicious lesion in cases of multiple lesions remains unclear, and whether performing biopsy for each of the multiple lesions identified by mpMRI provides additional information for the detection of csPCa is still a matter of debate [26]. Stabile et al [27] proposed that the combination of SBx and TBx for all lesions identified by mpMRI yielded the highest detection rates for both PCa and csPCa. Yet, the addition of TBx for secondary lesions increased the detection of csPCa only marginally. The study suggests that, for men with more than one visible lesion detected by mpMRI, a biopsy approach limited to SBx plus TBx of the most suspicious lesion may be more efficient, reducing procedure duration and potential complications. Patel et al [26] focused on a population of 381 men with positive mpMRI and suggested that the presence of multiple suspicious lesions at mpMRI was not correlated with increased detection of csPCa. Therefore, additional TBx of secondary lesions can be omitted theoretically.

3.2.5. *ROI location*

A noteworthy development in the context of detecting anterior/transition zone (TZ) lesions is the widespread diffusion of TP prostate biopsy. Initially gaining traction due to its proven effectiveness in reducing infectious complications [28], TP biopsy has evolved, with recent studies indicating that MRI fusion biopsy (MRI-TBx) conducted through the TP approach may exhibit superior capabilities in detecting csPCa within the TZ [19]. It has been postulated that the enhanced detection observed in these studies is attributed to improved sampling using TP approaches, thereby suggesting potential advancements in csPCa identification within the TZ [19,20]. Some studies have previously explored the detection rates of csPCa in the TZ and peripheral zone (PZ) within the PI-RADS categories. Mehralivand et al [29] highlighted a diminished detection rate of csPCa in the TZ compared with PZ PI-RADS 5 lesions (66.7% vs 76.3%). Similarly, in a comparative analysis of the diagnostic accuracy of PI-RADS v2.0 and 2.1 in the TZ and PZ, Rudolph et al [30] revealed inferior specificity for TZ lesions, with an overall lower detection rate for csPCa in PI-RADS 5 lesions located in the TZ (59.3% vs 72.1%). Four-core eTBx of lesions in the inner sectors of the prostate had lower sensitivity (59%) than that in the outer sectors (78%). The four-core eTBx template had higher sensitivity in the anterior (83%) than in the mid and posterior sectors (71%), suggesting that four-core eTBx may suffice for large, highly suspicious anterior lesions in small or slightly enlarged prostates [5]. Of note, among patients with PI-RADS 4 and 5 lesions, the location of the biopsy was not associated with the detection of csPCa [4].

3.2.6. *PI-RADS score*

Ahdoot et al [31] evaluated how to optimize the strategy for diagnosing aggressive PCa in men with abnormal prostate MRI scans, while minimizing the risk of unnecessary biopsies. The investigation utilized the PI-RADS scoring system for MRI images. The results showed that among cases with a PI-RADS score of 5, nearly all csPCa cases were detected by TBx, with SBx providing only a marginal increase in detection. In contrast, for PI-RADS 3–4 cases, the addition of SBx significantly increased csPCa detection compared with TBx alone. The study concluded that while a combination of biopsies increases csPCa detection, the benefit is observed primarily in PI-RADS 3–4 lesions. The suggested strategy is to use TBx alone for PI-RADS 5 lesions, avoiding excess biopsies, and to employ a combination of TBx and SBx for PI-RADS 3–4 cases, ensuring a low risk of missing csPCa cases. This approach emphasizes the importance of tailoring biopsy strategies based on the PI-RADS score, optimizing diagnostic accuracy while minimizing unnecessary procedures. For PI-RADS 5 lesions, sampling beyond four cores did not improve the detection of GG $\geq$2 disease. It is noteworthy that the PI-RADS score of secondary lesions was not associated with the csPCa detection at overall TBx [27].

3.2.7. *Learning curve*

The learning curve for operators should also be considered for all biopsy techniques. Equivocal data are available in the literature about the number of biopsies to be performed during the learning curve (ranging from 100 to 1500 biopsies) [32]. In the first 100 biopsies, an operator might need to acquire an increased number of targeted cores, as

improved detection of csPCa is achieved by taking four or five cores during this period [32]. In the context of previous studies, it has been documented that the learning curve typically levels off after completing approximately 50 cases [33,34]. There is also a learning curve for radiologists. It is essential that images be reviewed by dedicated expert radiologists who perform a minimum number of examinations per year, using standardized reporting systems. In cases where international recommendations are not followed, it is reasonable to consider increasing the number of TBx cores. Confidence in accurately targeting the tumor during biopsy is crucial, especially when no "safety net" SBx are performed.

The dual approach of TBx and SBx helps mitigate the limitations of each method when used alone, ensuring a more comprehensive and reliable diagnosis of PCa. This is particularly important in cases where MRI or TBx is not fully reliable due to operator-dependent or operator-independent factors. Improvements in software and technique could enhance operators' confidence in hitting the tumor, thereby boosting targeting performance. Furthermore, a quality reporting system for the urologist's performance in SBx and TBx would be helpful, as the quality of TBx becomes more important when no SBx is performed. This would improve reliability and confidence in treatment planning based on biopsy results.

3.3. Pain control and complications

A comparative study was conducted to evaluate the pain and anxiety levels among patients undergoing SBx (12 cores, 99 patients) versus SB + TBx (12 cores + two to four cores for each target, 66 patients). The SBx + TBx group encountered a greater number of biopsy cores (16.2 vs 12) and prolonged procedure times (23 vs 10 min). Compared with the SBx + TBx group, patients in the SBx group reported significantly less postprocedural anxiety, evidenced by a mean difference of –7 (p = 0.001) due to a significantly lower number of biopsy cores. TBx is associated with an increase in patient discomfort, affecting up to 28% of patients (discomfort level of 7–10), and heightened anxiety, experienced by up to 15% of patients (anxiety level of 7–10) [35].

Thus, reducing pain and anxiety in MRI-TBx procedures hinges not only on the total number of biopsies performed, but also on the practitioner's experience and the efficiency of the procedure. To attain clinical expertise in detecting csPCa, a learning curve of 25–45 procedures is necessary. Notably, 84% of patients reported pain scores between 0 and 1, with a proficiency plateau, marked by consistent performance in timing, detection accuracy, and pain management, being reached after 20 to 100 cases [34].

Recent studies emphasize the critical role of optimizing biopsy core numbers and selecting appropriate techniques to minimize infectious complications post-prostate biopsy. In a comparative analysis of TR-SBx and TR-TBx, both methods had comparably low rates of severe infections. However, TR-TBx, which requires fewer cores (3.7 vs 12), was linked to a lower incidence of minor infectious complications, such as positive urine cultures and elevated C-reactive protein levels. This suggests that minimizing biopsy cores could effectively reduce postbiopsy infection risk [36]. Similarly, in a comparative study of three MRI-based prostate biopsy techniques [37], the TR IB-MRI-TBx method showed fewer complications, primarily because it avoids additional SBx.

According to a study by Tops et al [37], to lower the infection risks following prostate biopsies, the number of cores in TR procedures should be reduced, or TP biopsy techniques should be considered. This research, covering 4233 biopsies from 3707 patients, showed that the conventional TRUS-guided biopsy method, using around 12 ± 1.4 cores, resulted in a 4% and 4.8% infection rate within the 1st week and the 1st month, respectively. Conversely, the TP approach using MRI-ultrasound fusion guidance, which involves 16 ± 3.7 cores, decreased the occurrence of infections substantially by 71% and 56% within 7 and 30 d, respectively. Furthermore, within the TR techniques, opting for fewer biopsy cores through MRI-ultrasound fusion or direct MRI guidance showed fewer complications than the standard TR-TBx [37].

In a prospective multicenter study investigating the effect of the number of biopsy cores (mean 25.4 ± 7.6) on complications following TP-TBx without antibiotic prophylaxis, an increased number of cores were associated with a higher incidence of overall complications (OR 1.08, 95% CI 1.02–1.14, p = 0.01), specifically bleeding complications. However, there was no significant association between the number of cores and infectious complications (OR 1.03, 95% CI 0.97–1.10, p = 0.6) [38].

3.4. Unmeasured factors and open questions

There are still unresolved questions that need addressing. Improving cancer detection corresponds to more cancers being labeled as significant, the prognostic significance of which still needs to be proved. Furthermore, fewer cancers are labeled as insignificant (potentially the same tumors but better sampled), which may lead to overtreatment. Additionally, adjusting the number of biopsy cores on a case-by-case basis introduces complexities. Increasing the number of cores for a small lesion could result in a stage shift, complicating the comparison of prognoses. It is likely that MRI has introduced significant grade inflation, and the threshold for csPCa should be raised significantly. The use of MRI-TBx has led to grade migration, potentially raising the GG and shifting what constitutes a "significant" cancer [39]. This could lead to an overestimation of cancer severity and impact treatment decisions. Raising the definition of csPCa might lead to fewer patients qualifying for aggressive treatments, which could reduce overtreatment without compromising outcomes. Increasing the number of cores, especially the nontargeted cores, significantly increases overdiagnoses with related patient harm.

The balance between the benefit and harm is precarious, and can tilt quickly in the wrong direction if the number of cores is increased unnecessarily. In fact, there are no data supporting the patient benefit of curative treatment for cancers detected in the MRI era.

It must be emphasized that the definition of csPCa is vague in the literature. We commonly define csPCa as International Society of Urological Pathology (ISUP) GG ≥2, but important variables are often omitted from the definition of csPCa, such as the number of positive cores, location of positive cores in the gland, ratio between TBx and SBx, concordance between TBx and SBx, percentage of ISUP >1 per core, core involvement with ISUP 1 ≥50%, total tumor length as a percentage of the total core length of the index lesion, and presence of histological variants. This also suggests a need for a more stringent definition of csPCa, one that considers long-term outcomes and real patient benefits rather than merely the pathological upgrades observed in biopsies.

The significance of gathering and utilizing local data highlights the need for decision-making tools, such as nomograms, to integrate data from TBx. This should include local rates of postbiopsy infections and positive predictive values for various types of lesions. Incorporating this specific information will allow health care providers to customize diagnostic and treatment strategies to align with the unique characteristics of the local patient population.

4. Discussion

The exploration of factors influencing the number of targeted cores during prostate biopsy reveals a complex landscape shaped by different features. Figure 1 illustrates the multifaceted approach required to determine the optimal number of MRI target cores. It highlights the interplay between lesion characteristics, prostate size, PI-RADS scores, and other critical factors, emphasizing the need for a personalized strategy that ensures diagnostic accuracy. The absence of definitive standardization in biopsy planning underscores the importance of optimizing strategies to enhance cancer detection while minimizing unnecessary procedures.

From a clinical standpoint, our results highlight that five cores should be taken per ROI to improve the detection of csPCa without increasing the risk of complications substantially. Moreover, other factors such as penumbra sampling, MRI ROI location, and urologist experience should be considered when planning the optimal number of biopsy cores during MRI-targeted approaches.

However, the previously mentioned variability in external variables to the number of cores per index lesion introduces a significant challenge, potentially affecting the

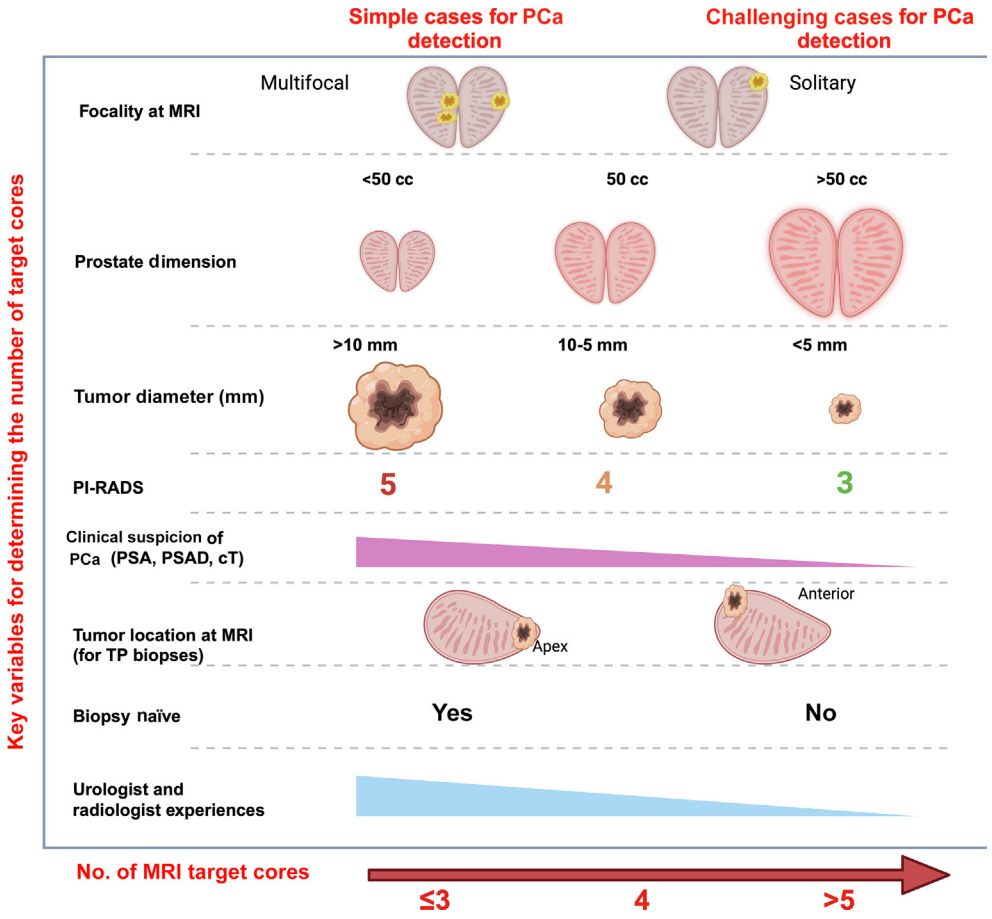

Fig. 1 – Guiding variables for determining the number of MRI-targeted biopsy cores. Each variable is presented as an ideal and a challenging case. MRI = magnetic resonance imaging; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSADT = PSA doubling time; TP = transperineal.

study's outcomes. This inconsistency represents a substantial limitation of our research, as it precludes the precise determination of our findings' relative significance due to unadjusted confounding factors. While a case-specific biopsy core strategy could potentially offer more precise cancer staging by accounting for the variable aggressiveness of cases, it also introduces considerable challenges in comparing outcomes and requires the development of new risk stratification models tailored to each biopsy approach. Thus, the benefits of comparability and simplicity in risk stratification provided by a standardized approach might outweigh the potential gains of individualized biopsy strategies.

Despite being one of the first attempts to summarize available evidence on the optimal number of biopsy cores in patients undergoing MRI-targeted approaches, our review is not devoid of limitations. First, due to the low number of randomized controlled studies available in this field, we decided to perform a narrative review of the literature. Second, most of the included studies have been performed in high-volume centers, where the performance characteristics of mpMRI and MRI-TBx are higher and, therefore, their generalizability is not warranted in other settings.

5. Conclusions

Determination of the optimal number of cores for targeted prostate biopsies involves balancing the need to minimize sampling errors with ensuring comprehensive cancer detection, tailored to the individual characteristics of each patient and his prostate. It is advisable to consider up to five cores per MRI target—perilesional area during MRI-TBx to enhance the detection rate of csPCa. However, the specific number of cores should be customized based on various factors, including the strategy of the biopsy, prostate and lesion volume, PI-RADS score, biopsy techniques, potential complications, and patient discomfort during the procedure. Given the various factors influencing the number of targeted cores during prostate biopsy, further research and standardization are crucial.

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Study concept and design: Zattoni, Gandaglia.
Acquisition of data: Fasulo.
Analysis and interpretation of data: None.
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