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INVITED REVIEW

Controversies in MR targeted biopsy: alone or combined, cognitive versus software-based fusion, transrectal versus transperineal approach?

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Abstract

Purpose To review the evidence addressing current controversies around prostate biopsy. Specific questions explored were (1) mpMRI targeted (TgBx) alone versus combined with systematic (SBx) biopsy; (2) cognitive versus software-based targeted biopsy; (3) transrectal or transperineal route (TP).

Methods We performed a literature search of peer-reviewed English language articles using PubMed and the words "prostate" AND "biopsy". Web search was implemented by manual search.

Results Prostate mpMRI is revolutionizing prostate cancer (PCa) diagnosis, and TgBx improves the detection of clinically significant (cs) PCa compared to SBx alone. The utility of combining SBx–TgBx is variable, but in non-expert centres the two should be combined to overcome learning curve-limitations. Whether SBx should be maintained in expert centres depends on what rate of missed cancer the urological community and patients are prone to accept; this has implications for insignificant cancer diagnosis as well. TgBx may be more precise using a software-based-approach despite cognitive TgBx proved non-inferior in some studies, and may be used for large accessible lesions. TP-biopsies are feasible in an in-office setting. Avoidance of the rectum and accessibility of virtually all prostate areas are attractive features. However, this has to be balanced with local setting and resources implications. Ongoing trials will shed light on unsolved issues.

Conclusion The prostate biopsy strategy should be tailored to local expertise, needs and resources availability. Targeted biopsy enhance the ratio between cs and insignificant cancer diagnosis, although some csPCa might be missed. Software-based TgBx are likely to be more precise, especially for new users, although the additional cost might be not justified in all cases. TPBx have ideal attributes for performing TgBx and avoiding infection, although this has resources implications.

Keywords Prostate biopsy · MRI · Targeted biopsy · Transperineal · Transrectal · Cognitive

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Introduction

Prostate cancer (PCa) histological sampling to provide definitive diagnosis remained widely unchanged for over 40 years. Since Hodge and associates introduced the concept of systematic blind sampling of the prostate gland, little has changed [1]. It is now well known that increasing the number of cores over certain thresholds does not increase the diagnostic yield of clinically significant (cs) PCa in the majority of cases, but does increase the biopsy-related morbidity [2–4]. As per recommendation of international guidelines [5, 6], the standard test currently remains a systematic transrectal-ultrasound guided 12-cores scheme (SBx) [7]. However, SBx schemes are limited by the related random and systematic errors. The random nature of this strategy lacks of reliability as the sampling of

cancerous areas is linked to chance; the systematic error is related to the undersampling of certain areas of the prostate—such as the anterior area and the apex. From a critical perspective, SBx miss approximately 20% of csPCa [8], determining underdiagnosis, and eventually undertreatment. In addition, SBx can inadvertently detect insignificant PCa causing overdiagnosis, and eventually overtreatment [3–6, 9].

In the last decade, multiparametric prostate MRI (mpMRI) is gradually revolutionizing PCa diagnostics due to its ability in detecting and ruling out csPCa [9, 10]. In other words, mpMRI offers the opportunity of locating and targeting cancerous areas as for all solid organs including liver [11], thyroid [12], kidneys [13], lungs [14] and many others where, instead of randomly hitting the whole parenchyma, only suspicious areas are sampled (Targeted biopsy—TgBx).

However, the new standard for prostate biopsies may still be a long way off as several questions remain unsolved.

First, mpMRI can still miss csPCa [15, 16]. The optimal sequence and combination of tests is a matter of debate. Should we do SBx first, TgBx alone first or should we still rely on a combination of the two strategies, systematic and targeted? Whilst some already advocate TgBx only to reduce overdiagnosis and to improve detection of csPCa [17, 18], others argue SBx must be carried out to complement targeted ones [19, 20].

Second, mpMRI TgBx can be performed in a cognitive manner or using a fusion software [21]. The former strategy relies on a skilled operator able to register the MR images over the real-time transrectal ultrasound to target the suspicious region/s of the prostate; the latter strategy relies on a fusion device performing an overlap of MR images over real-time TRUS to visualise a target for selective sampling. The sheer amount of different "fusion" devices available on the market further complicates the comparison between cognitive and software-based approaches.

Third, the approach to the prostate is another matter of debate. In the era of antibiotic resistance should we use the transperineal (TP) or the transrectal (TR) route? Some argue in favour of transrectal biopsies suggesting higher deliverability in healthcare settings and lower resources requirements, whilst others maintain the superiority of the transperineal approach, mainly to reduce infections and in light of unlimited access to virtually all areas of the gland. [22].

We performed a systematic literature review summarizing the latest evidence on different biopsy strategies to shed light on the aforementioned areas of debate.

Materials and methods

We performed a non-systematic web search to include most relevant English peer-reviewed articles from 1st January 2000 to 1st April 2018 using PubMed and the words "Prostate" and "Biopsy" pooled together with the boolean operator "AND". Manual search of the references of included articles was also performed. Additional records and important ongoing studies were also considered based on senior authors consultation. We 'a priori' excluded retrospective studies with less than $n = 50$ patients and/or reporting "in-bore mpMRI-targeted biopsy" results only. Most relevant articles to answer the three main review questions were selected by two authors (G.M, M.V.). A third author (G.P.) solved discrepancies. Evidence synthesis is organized to separately address the three relevant questions: (1) TgBx and/or SBx; (2) cognitive versus software-based targeted biopsy; (3) transrectal versus transperineal route.

Evidence synthesis

MRI-TgBx versus SBx biopsies (Fig. 1)

Prostate mpMRI detection of csPCa ranges from 44%, in biopsy-naïve, to 87% in prior negative biopsies, and has a NPV in excluding csPCa ranging from 63% to 98% [10]. Recently, the PROMIS trial, a multicentre paired-cohort confirmatory study comparing mpMRI and SBx using transperineal template mapping biopsies as the reference test in 570 men, proved that mpMRI has significantly higher sensitivity (93% vs 48%) and NPV (89% vs 74%) for csPCa. Using mpMRI as a triage test in biopsy-naïve patients would allow approximately a quarter of men at risk to avoid biopsy, reducing the diagnosis of non-significant PCa, and improving detection of csPCa [23]. Whilst level 1 evidence in favour of mpMRI is likely to further increase the rates of patients presenting with a positive mpMRI, thus seeking an image-guided sampling, TgBx in men with a positive MRI were not performed in PROMIS as the aim of the study was to assess diagnostic efficacy of mpMRI alone. Nonetheless, other studies have investigated the diagnostic performance of TgBx against SBx in patients with suspicious mpMRI.

The first issue is whether TgBx alone improves csPCa detection as compared to SBx in an initial or a repeated biopsy setting.

A systematic review investigating the role of MRI targeted biopsies found that TgBx detect more csPCa (median 33.3% vs 23.6%) using fewer cores (median 9.2 vs 37.1) compared with SBx. In terms of utility, namely the percentage of men with csPCa missed by one strategy and detected by the other, a median of 9.1% additional csPCa that would have been missed by SBx were detected by targeted sampling [24]. Siddiqui et al. assessed 1003 men with two separate blinded physicians performing TgBx and SBx, respectively. Detection rates were similar; however, TgBx diagnosed 30% more high-risk ($p < 0.01$) and 17% fewer low-risk PCa ($p < 0.01$) [17].

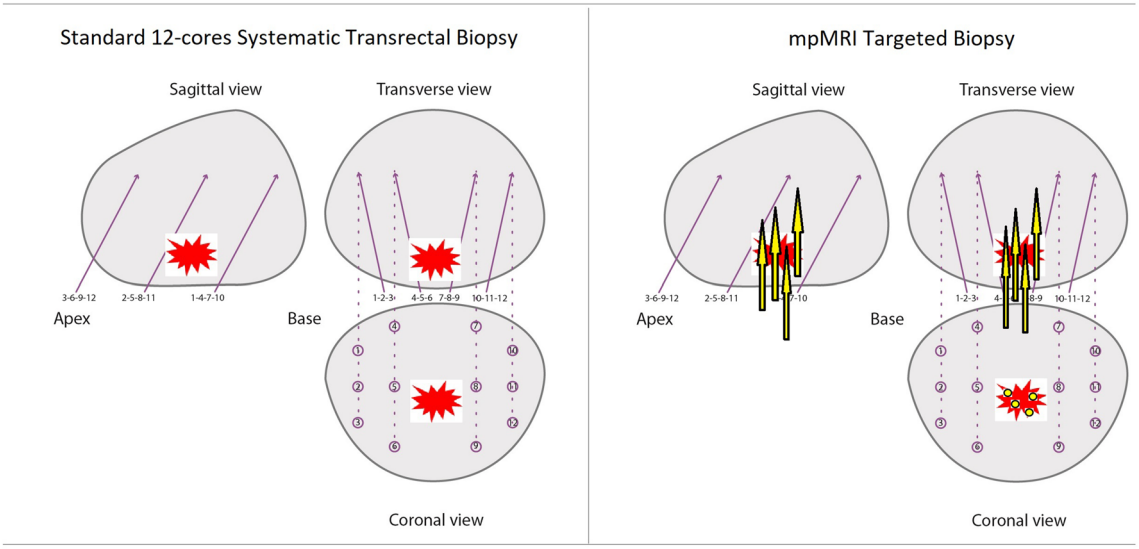

Fig. 1 Graphical representation of systematic and mpMRI-targeted transrectal biosy schemes with an apical right posterior suspicious area (in red). Left: transrectal 12-cores standard sampling. Right: mpMRI-targeted biopsy scheme with a 4-cores sampling of the suspicious area

In a meta-analysis of 16 studies ($n = 1926$ men) with positive MRI, TgBx and SBx did not significantly differ in overall PCa detection. However, TgBx detected 20% more csPCa and avoided almost twice the number of insignificant PCa compared to SBx. Interestingly, subgroup analysis confirmed TgBx superiority only in men with previous negative biopsy, rather than in men with initial biopsy. Nonetheless, the authors found a much higher SBx sensitivity in biopsy naïve men (65%) compared to the literature. This may have influenced the results causing a non-significant difference [25].

Finally, some single center studies randomizing men to an mpMRI-based pathway with subsequent TgBx in case of positive MRI versus SBx showed conflicting evidence [18, 26–29]. Results of a multicentre non-inferiority RCT, the PRECISION trial, were recently published. The study randomized 500 men in a 1:1 ratio to an mpMRI pathway with subsequent TgBx alone (no SBx) in case of suspicious findings versus first line SBx. Overall mpMRI-based pathway detected more csPCa (38% vs 24% in the SBx arm; $p = 0.005$) and less insignificant PCa (9% vs 22% in the SBx arm; $p < 0.001$). Taking fewer biopsy cores in the mpMRI group (median of 4 vs 12 cores per patient) also proved benefits of in terms of comorbidities as less complications were recorded compared to SBx group [30]. Follow-up of negative patients is needed to further define the added value of the mpMRI-based pathway.

Overall, level 1 evidence now suggests that TgBx improve PCa detection and risk stratification compared with SBx.

The second issue is whether combined random cores improve csPCa detection compared to TgBx only. In other words, do we still need to perform SBx along with TgBx?

Whilst some advocate that a pure imaging-based pathway relying on TgBx only would reduce overdiagnosis [18], others do recommend to maintain complementary systematic cores as some csPCa may still be missed [27, 31].

General consensus has been reached that the combination of TgBx and SBx should be currently considered as the most detailed detection evaluation, [6, 19] given the inherent imprecision of exclusive image-guided biopsy.

The PRECISION trial proved TBx alone yield significantly higher csPCa detection compared to SBx. However, as this was a RCT, and those men assigned to the imaging pathway did not have random biopsy, we do not have information regarding csPCa being missed by TgBx [30].

Contrasting evidence also derives from systematic reviews and meta-analyses as detection of csPCa varies widely, suggesting TgBx alone would miss from to 2.1 up to 15% of csPCa, according to the prevalence of disease in the study population and the biopsy strategy [21, 24, 25, 32, 33].

Baco and colleagues randomized 186 men to mpMRI TgBx plus SBx versus SBx and found two cores TgBx had csPCa detection comparable to SBx in the same patients and in the control group. In the mpMRI group 5 on 51 csPCa (10%) were by missed by MRI and/or TgBx. Authors concluded a 2-cores TgBx may replace SBx [18].

Siddiqui et al. found that adding SBx to TgBx increases overall cancer detection (10.2%; $n = 103/1003$). However, 83% were low-, 12% intermediate-, and only 5% were high-risk PCa, respectively [17]. Similar findings in a secondary biopsy setting were confirmed by others, with TgBx having overall similar PCa detection compared to SBx but being more likely to find csPCa [34].

Despite lowering insignificant PCa and improving csPCa diagnosis, TgBx alone still miss some csPCa [8, 17, 31, 35, 36]. Some reported low rates of missed csPCa, but still suggested the need of concomitant SBx [31, 35]; according to a recent report, up to 1 on 10 men harbouring csPCa may be missed if not performing SBx, especially in case of cancers being located at the apical and/or dorsolateral and apical regions [8].

Nonetheless, others suggested the price to pay to diagnose these additional cancers may be higher than expected as a large study by the NIH reported sixty patients need to have SBx in addition to TgBx to diagnose one csPCa. The number goes up to 200 patients to diagnose one high-risk PCa [17].

The degree of csPCa missed by TgBx can be influenced by several factors including center/operator experience in the different interdependent steps of an imaging-based strategy (image acquisition, imaging interpretation, registration and targeted sampling [19, 37]) as well as csPCa prevalence in a given population, as mpMRI NPV significantly diminishes if prevalence increases [38].

Oderda et al. just published the largest TgBx series to date including 2115 men from 15 centers in four European countries. Primary aim of the study was to overcome the limitation of highly experienced single center studies and to frame results of daily routine practice in mpMRI TgBx. Detection of csPCa was 43% overall for TgBx with SBx. However, 9% of csPCa were detected by SBx only. In other words, one in five men harbouring cs disease would have been missed by TgBx [39]. These results strengthens current expert recommendations of recent consensus panels [19, 20] and other studies [40, 41] stating in daily practice TgBx should be performed along with SBx.

Finally, besides pure diagnostic considerations, adding SBx–TBx allows a more accurate mapping by sampling also non-mpMRI-suspicious areas [42]. The choice of performing additional random sampling may also depend on patient- and centre-related treatment opportunities. The need of excluding mpMRI invisible csPCa is key when considering the raising interest towards tissue sparing approaches [43, 44].

The ideal biopsy technique should optimize detection of csPCa whilst minimizing comorbidity and costs. However, the paramount issue remains determining the effectiveness of the approach selected. Both TgBx and SBx are not perfect and may miss some csPCa. Using a combination of the two approaches increases cs but also non-csPCa diagnosis. Hence, the crucial point is the rate of missed csPCa we can accept, and at which cost. Probably, the correct answer to our needs lies halfway. To date we are in the beginning of the dissemination of mpMRI and TgBx across the board; over time, climbing the learning curve may improve outcomes [45]. Therefore, whilst TgBx should be performed together with SBx in non-experienced centers, others may decide not to perform SBx based on their own results, and their confidence with the TgBx approach [8, 19].

To conclude, in view of TgBx now being the standard of care, a third issue is how many targeted cores should be obtained from the index lesion.

It is generally advised to obtain at least 2 cores per target, adding samples depending on lesion size and location as well as operator expertise [19]. However, evidence is currently limited to a small number of studies.

A recent analysis of 418 men undergoing fusion TgBx using two cores investigated the impact of the second targeted core: 21 on 191 more PCa diagnoses were made and 10% of PCa were upgraded to a higher Gleason score. However, only 12 of these additional diagnoses were csPCa [46]. Similar findings were reported by the same group when assessing the impact of a second targeted core using an in-bore TgBx technique [47]. Authors concluded obtaining more than one biopsy per lesion provides only a slight improvement [46, 47].

Contrarily, Porpiglia and co-workers suggested two fusion targeted biopsies directed in the middle of the lesion should be performed, obtaining a 92.5% accuracy compared to four to six targeted biopsies in case of a positive lesion. Usefulness of a second core was more marked in case of mpMRI-heterogeneous lesions [48].

Others investigated three and four targeted cores models with computer simulation analysis using whole-mount reconstructed radical prostatectomy specimens. Four compared to three targeted cores TgBx did not significantly improve maximum cancer length, slightly reduced the percentage of positive cores and increased of approximately 10% the correct classification/identification of high-risk cancers [49].

Again, as per the addition of SBx–TgBx, we do believe the optimal number of targeted cores should be decided depending on centre experience, as well as the treatment implications of the diagnostic strategy. In centres in which tissue-preserving approaches—active surveillance and focal therapy—are proposed, the added valued of zonal distribution of disease seems more relevant.

Nonetheless, whilst performing SBx in addition to TgBx would at least triple the number of cores taken, leading to a total of 13 up to more than 20 cores depending on the number of targets and of TgBx per target, the issue is different when considering TgBx only.

Whilst each additional core certainly increases costs [50], its impact in terms of patient pain and complications has never been practically assessed. Although it seems unlikely a few additional biopsies may have a clinically quantifiable and significant impact, given the widely investigated low morbidity of 12-core SBx, this certainly needs further investigation.

Cognitive versus software-based TgBx (Fig. 2)

Cognitive TgBx is attractive as it is quick, easy to perform and has limited cost as no fusion-platform device is required, neither the time to register the MR images over the TRUS. However, is the human brain able to achieve the same results of sophisticated fusion softwares? Current evidence is conflicting.

A systematic review suggested software-based TgBx detect clinically significant disease more than visual TgBx (20.3% vs 15.1%) [24]. Others supported similar conclusions [51, 52]. Delongchamps and associates evaluated TgBx in 391 men divided in three consecutive cohorts undergoing elastic, rigid and cognitive techniques, respectively. Rigid and elastic TgBx improved csPCa detection compared to SBx ($p < 0.05$), whilst cognitive TgBx did not ($p = 0.66$). Detection of PCa undetected by SBx was also significantly lower for cognitive TgBx [51]. Differences may be more marked for lesions < 10 mm [52].

Opposite results are also available. A meta-analysis by Schoots et al. did not find any difference in overall and csPCa detection between cognitive and fusion-based TgBx [25].

Direct comparisons of the two targeted approaches in the same group of patients are few. A French multicentre study, not included in the previously cited meta-analysis, revealed no differences in overall and csPCa detection, even when stratifying by lesion location and volume [53]. Nonetheless, only 68 of 95 men underwent both approaches which may have caused under-powering and all TgBx biopsies were performed by the same operator under radiologist's supervision.

Contrarily, in the PROFUS Trial, 125 patients underwent two TgBx cores by one operator under software guidance and then two cognitive TgBx cores and SBx taken by a second physician, blinded to the previous procedural phase. Despite no overall PCa detection differences, the software-based approach was more histologically informative detecting 77 targets compared with 60 by cognitive TgBx ($p = 0.01$) and improved accuracy for smaller lesions. Authors suggested a larger number of patients may have resulted in an even greater magnitude of benefit in favour of software-based TgBx [54]. Others compared the two approaches in 50 consecutive men subsequently undergoing transperineal template mapping biopsies. Despite differences were not statistically significant efficiency and utility were slightly in favour of the software based strategy; interestingly, a combination of the two approaches would have resulted in a reduction of missed csPCa [55].

To note, a trial randomizing men to an MRI diagnostic pathway with subsequent SBx plus TgBx versus SBx only found no significant differences in csPCa detection overall and in the MRI group using a cognitive TgBx approach [27].

Wegelin et al. investigated whether one TgBx technique performs better than the others in a recent meta-analysis: no significant differences were highlighted in the detection of csPCa amongst cognitive and software-based approaches [21]. Does this mean we should do cognitive biopsies?

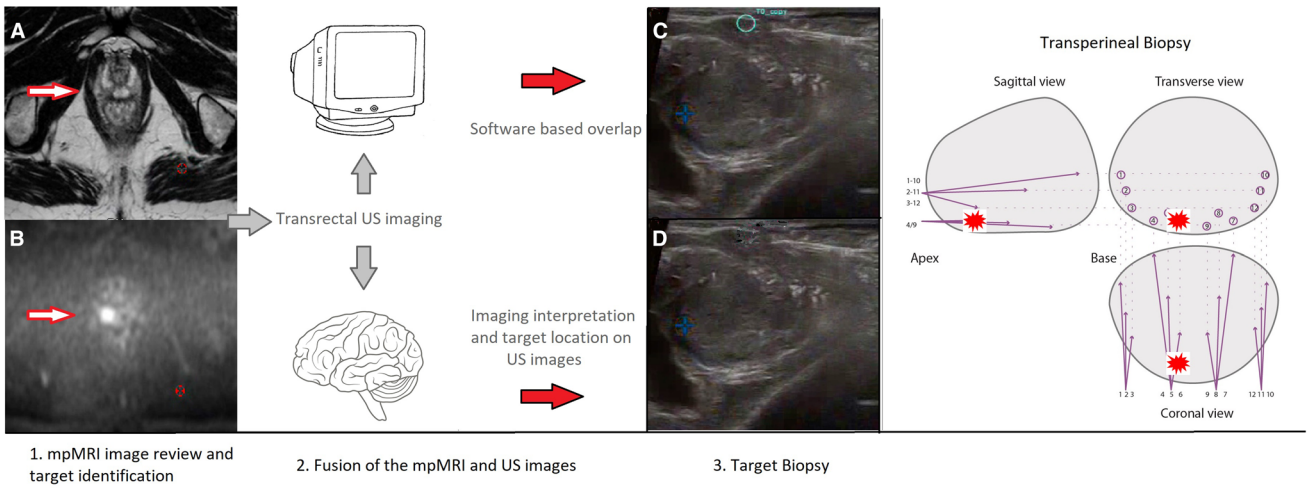

Fig. 2 Software-based and cognitive mpMRI-targeted biopsy techniques. In the image, biopsies are performed in a transperineal fashion. 1. = First step: mpMRI images are reviewed (A. transverse T2-W image showing a small hypointense lesion in the right apical part of the gland; B. DWI image showing the same lesion as an hyperintense area). 2. Prostate ultrasound images are then seen using a transrectal probe and software-based overlap versus mental location of the target by the operator are performed, respectively. 3. A biopsy needle takes a sample in the targeted area (C. target resulting from a software-based overlap of the images is highlighted in the US image; D. a cognitive core is taken in the area identified as the corresponding US location of the mpMRI-suspicious area). Additional systematic cores can then subsequently be taken depending on institutional protocol. On the right a graphical representation of a transperineal mpMRI-targeted biopsy scheme

Unfortunately, several factors do not allow definite conclusions.

The overall number of patients and available studies is small, especially for the cognitive biopsy. For instance, in the aforementioned analysis, despite including seven and fourteen articles investigating cognitive and fusion TgBx for a total of 712 and 2817 men, respectively, only a minority assessed csPCa ($n = 220$ cognitive TgBx) and were evaluated. In agreement with this the majority of studies assessing cognitive biopsies have a relatively low number of patients, rarely reporting outcomes for more than 150 men [21].

Further, the quality of studies reporting on cognitive biopsies is also low. Only a few prospectively investigated outcomes on the same patients and to our knowledge no large specifically designed head-to-head RCTs amongst cognitive and fusion biopsies are available to date. Absence of mpMRI lesions characteristics, use of different MRI protocols and csPCa definitions further hampers results interpretability.

Moreover, there is room of operator expertise and learning curve-related bias. Prostate motion may cause sampling and registration errors, possibly affecting outcomes, especially in case of small lesions; filling-related rectal and bladder motion, patient position, use of endo-rectal coil and/or US probe, patient movements due to pain are some of the several factors possibly influencing cancer detection. Accuracy of three-dimensional MRI/US registration has an estimated target registration error of 2.4–2.5 mm [56, 57]. Using elastic registration, errors may be further reduced [58].

On the contrary, operator-related targeting errors have never been assessed for cognitive biopsies and the risk of human error is hard to be quantified as it is per definition subjective. Locating the mpMRI target in the US prostate requires highly demanding cognitive registration ability, especially for some areas of the prostate, for small targets, and/or large glands [59]. Whilst several groups investigated the learning curve for software-based TgBx [45, 60–62], to our knowledge only one small single centre series assessed cognitive TgBx learning curve of a single urologist [63], claiming the need for further evidence to appropriately address the operator's expertise impact on csPCa detection.

Importantly, it is relevant to consider patient digital and personal data storage advantages of software-based devices. The ability of browsing sites of previous sampling may be key when performing re-biopsy of men with a previous negative histology and persistent PCa suspicion or in active surveillance cohorts. Furthermore, this feature is indeed helpful in local treatment planning including whole-gland or focal ablative energies and, although it has yet to be assessed, may improve therapeutic precision.

Finally, software-based fusion approaches may improve csPCa detection rate and may reduce the learning curve necessary for visual targeting as their accuracy may be superior to a cognitive TgBx. Whilst the greatest impact of fusion TgBx is generally found when targeting small lesions and/or larger glands, a cognitive approach may be adopted for large lesions, which are easier to detect [64]. This with the essential requirement of expert operators as otherwise TgBx may not improve csPCa compared to SBx.

A three arm multicentre-RCT, the FUTURE trial, is currently randomizing men with persistent PCa suspicion after at least one prior negative biopsy to software-based fusion, cognitive or MRI in-bore TgBx, respectively. This trial will clarify the role of cognitive biopsy in PCa diagnosis [65].

Transrectal versus transperineal route (Fig. 3)

Since Emiliozzi et al. published their series of transperineal freehand biopsies 15 years ago [66], the debate over potential advantages of the perineal route remained open. To date, no robust RCT has been completed to address this important question. The debate has now switched to the utility of one approach over the other, in the context of TgBx. The key issues to consider are the infection rate, the deliverability in the outpatient setting, and the accessibility with special attention to the location of the tumour.

Some believe we have already entered a "post-antibiotic" era due to overuse and inappropriate antibiotic prescriptions [67]. The perineal route avoids rectal bacteria inoculation in the prostate as the perineal skin can be easily disinfected with appropriate antiseptic solutions and, therefore, the infection rate is minimal when a transperineal approach is preferred.

An analysis of the Rotterdam arm of the European Randomized Study for Screening for Prostate Cancer trial involving 10,474 prostate biopsies between 1993 and 2011 revealed as much as 4.2% and 0.8% having post-procedural fever and needing hospital re-admission, respectively. Later year of biopsy was the only factor associated with an increased risk of re-admission [68]. Similar findings were reported in other countries including UK, USA and Canada: post-TR biopsy infections are increasing; whilst ten years ago approximately 1 on 100 men had post-biopsy fever, now it occurs in up to 17.5% of the patients and up to 6.3% need hospital re-admissions [69]. These data are alarming, and should prompt adequate reaction.

Indeed, data well match with recent warnings against an increase in antibiotic resistant *Escherichia coli* and other bacteria of the rectal flora involved in urinary tract infections. One in five to almost one in two men harbours quinolones resistant bacteria at a pre-biopsy rectal culture [70, 71]; quinolones still remain the suggested drug for TR antibiotic prophylaxis by international guidelines [72, 73].

A recent AUA white paper on prostate biopsy complications suggested rectal culture and subsequent "targeted prophylaxis" or upfront antibiotic augmentation as possible strategies to reduce infections [72]. In particular, the latter

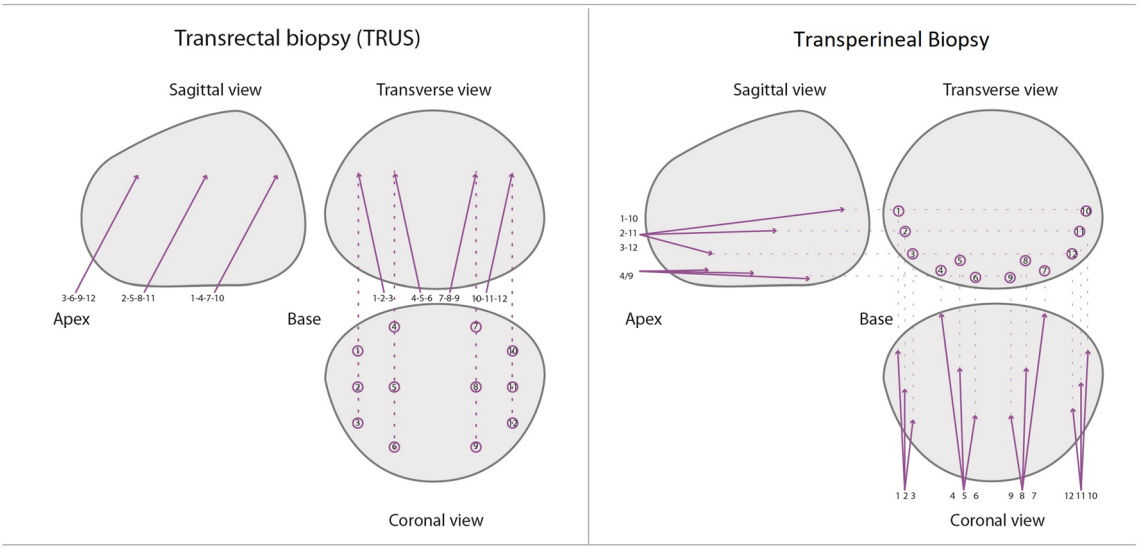

Fig. 3 Graphical representation of transrectal (left) and transperineal (right) systematic biosy schemes

option seems supported by several groups [71, 74]. In the last year, two studies even published their results assessing single dose carbapenem prophylaxis [75, 76]. But is heavier antibiotic coverage using a third line option and/or screening all men before TR biopsy the right answer to our needs? Whilst diminishing infectious rates in the short term, these strategies seem incoherent in facing the global warning on antibiotic abuse and will likely further increase resistance.

Another option to reduce infectious complications is TP biopsy. Many large studies were published with no or irrelevant infectious rates [77–80]. In a systematic review, the pooled analysis of 16 studies including 6609 men undergoing TP biopsies with up to 38 cores taken revealed a 0.076% ($n=5$) post-biopsy sepsis rate [80].

In a recent series of 43 men undergoing "antibiotic free" TP prostate biopsy no infections were described [81]. Despite to date no RCT proved superiority of TP over TR biopsies in terms of infectious complications the rising number of TP biopsy is no surprise, with as many as 38.5% of Urologists performing them in some countries [22]. From an infectious perspective, the TP approach may be thus preferred over the TR as it is likely to reduce if not to erase infectious related complications.

Second, is the issue of in-office feasibility. The TR route remains the most widely adopted as it is considered more deliverable from a resources' perspective. Some also claim low tolerability and higher comorbidity burdens for TP biopsies, which, in some series, are performed under general anaesthesia [4, 82, 83].

Hematuria, hematospermia, bleeding (rectal for TR and perineal for TP), rates of lower urinary tract symptoms and transient erectile dysfunction are highly variable and never proved any differences in favour of one of the two techniques. On the contrary, urinary retention occurrence was found slightly higher for TP biopsies by some authors, ranging from 1.7% to as much as 11.1% [70, 83]. Nonetheless, it should be noted: (1) many TP biopsy series used template mapping or saturation schemes; thus, the number of cores taken may have influenced reported retention rates compared to standard and TgBx protocols [70, 83, 84]; (2) several authors were not able to spot any significant differences in urinary retention between the two approaches [85]; (3) again, to date, no RCTs were able to highlight whether retention occurs more frequently using the TP or TR route.

Tolerability and procedural timings are other important points. Available evidence suggests overall TP Bx have high tolerability and low pain levels under local anaesthesia [85–87]; despite these analyses have never been performed as primary outcomes in a clinical trial no major differences are present between the two approaches when a similar number of cores is taken [83, 85]. Recent reports suggest TP route is not time consuming as a standard sampling can be easily achieved in less than 10 min [88]. To conclude, even in case of TR route, overall tolerability remains far from optimal. Rosario and co-workers prospectively evaluated 984 men undergoing 10-core TR biopsy within the ProtecT study: as much as 43.6% complained peri- and/or post-procedural pain, 17.5% fever, 65.8% haematuria and 92.6% hematospermia within 35 days after biopsy. Based on these findings, almost one on five patients would consider a major or moderate problem undergoing a further biopsy [89].

Finally, is the detection of csPCa. A recent report on MRI in-bore biopsies analysed the anatomical locations of missed PCa detected by TRUS and viceversa: most missed-cancers were located in the apex, dorsolateral and anterior prostate segments [8]. As pointed out by others, these are exactly the

locations for which the TP route provides an easier access [90].

Hence, the interest towards the TP approach remains high not only in terms of complications but also in terms of cancer characterization. Several fusion systems which allowed a TR sampling only are now allowing also a TP access [91]. Similarly, whilst the majority of TgBx studies are transrectal, reports on TgBx TP sampling are also growing [40, 41, 92, 93] and yielding cancer detection rates apparently not inferior to those of the TR route.

No differences between TP and TR routes in terms of PCa detection were shown on SBx; however, these findings may not be transferable to a TgBx context.

A single-center Italian study reported TP fusion TgBx as an independent predictor of csPCa diagnosis when compared to the TR route, in a multivariate model including PSA, rectal exam, prostate volume, PIRADS score, number of TgBx and operator expertise [63].

Pepe et al. compared TR fusion and TP cognitive TgBx both performed in 200 men undergoing mpMRI and TP saturation biopsy for persistent PCa suspicion after a negative TR SBx. Thirty percent had csPCa; of these, 78.3% and 93.3% were identified by TR fusion and TP-cognitive biopsies, respectively, ($p < 0.001$) with the TP cognitive biopsies showing higher sensitivity, specificity, PPV and NPV [94]. Nonetheless, the different TgBx methodology used is a non-negligible confounding factor hampering overall data interpretation.

To date, possible advantages of the TP approach in terms of csPCa detection remain theoretical only; there are currently no prospective comparisons in this setting. Large, prospective randomized studies comparing the two approaches should be strongly encouraged.

In summary, TP biopsy may offer advantages in terms of infectious related complications whilst it appears comparable to the TR approach for many other aspects including patients tolerability and other complications except for retention, which may be slightly higher for TP. Whilst in a SBx setting detection rates of PCa are equivalent, it remains to be clarified if any differences may be present in a TgBx setting. Indeed, a current lack of well-designed RCTs favouring one or the other approach has to be acknowledged.

Conclusions

Prostate mpMRI is revolutionizing prostate cancer (PCa) diagnostic pathway, questioning the optimal biopsy technique and strategy. TgBx improve csPCa detection compared to SBx. However, SBx along with TgBx represents so far the best available approach to reduce the risk of csPCa misdiagnosis. In an in-office setting software-based TgBx may improve csPCa detection compared to cognitive TgBx. Nonetheless, larger lesions could be targeted cognitively if an expert operator performs the biopsy. The transperineal route should be preferred over the transrectal as it may help in reducing infectious complications whilst it remains a tolerable procedure with other comorbidity burdens comparable to transrectal sampling. Ongoing and future RCTs will improve current evidence and help defining the optimal biopsy approach.

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