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CONSENSUS

Indications, strategies, and development on prostate targeted biopsy: Report of the Panjiayuan Consensus Conference 2022

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Abstract

Prostate biopsy is the gold standard for diagnosing prostate cancer (PCa). Prostate targeted biopsy (TB) having a higher rate of detecting clinically significant PCa (csPCa) than traditional systematic biopsy (SB) is supported by high-quality evidence. However, the TB indications and strategies are controversial. The National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, invited a panel of recognized urology experts in PCa to address these topics at the Panjiayuan Consensus Conference 2022. The conference results on prostate TB are presented herein. The National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences identified 10 key areas of prostate biopsy: (1) selection of imaging examination; (2) indications of TB; (3) transperineal and transrectal prostate biopsy; (4) TB pathways; (5) TB and SB; (6) three techniques of TB; (7) the number of TB cores needed for one lesion; (8) core number for SB; (9) free-hand TB; (10) future development of TB/prostate diagnosis. Thus, a panel of 25 recognized urologists and 2 radiologists from China were invited to attend this conference. The panel voted anonymously on 14 predetermined questions. Voting was based on the panelists' clinical practice and opinion, rather than high-level evidence. The voting outcomes were supported by the panel unequally, and details of the voting results were reported. The voting results can help clinicians to decide on biopsy timing and proper strategies, for which guidelines are sparse. We also focused on the future development of TB and SB, such as the combined pathway of TB and SB, techniques of TB, biopsy cores, free-hand TB, and prostate-specific membrane antigen positron emission tomography/computed tomography.

KEYWORDS

image-guided biopsy, magnetic resonance imaging, prostatic neoplasms

1 | INTRODUCTION

Prostate cancer (PCa) is the second most common solid tumor in men globally, with an age-standardized rate incidence of 31 per 100 000, causing a great burden of disease[1]. The prevalence of PCa is constantly rising in China, with approximately 153 400 cases in 2019, an incidence rate of 21.17 per 100 000, and an increase of 389% over 1990. To diagnose PCa, prostate-specific antigen (PSA) and digital rectal examination (DRE) are used for screening and early detection, multiparametric magnetic resonance imaging (mpMRI) is used to support diagnosis, and the gold standard for a definitive diagnosis is a histopathological examination of the prostate biopsy[2]. A biopsy is recommended for patients with a high risk of diagnosing clinically significant PCa (csPCa) in most international guidelines[2,3], whose recommendations on biopsy are rapidly updating, and prostate targeted biopsy (TB) is now considered having a higher rate of detecting csPCa than the traditional systematic biopsy (SB) in most studies. Although TB is admitted by studies, TB indications and strategies are controversial. In recognition of the importance of prostate TB, the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (located at Panjiayuan, Beijing, China), invited a panel of PCa experts in the fields of urology and radiology for a consensus conference to collectively discuss the indications, strategies, and development on prostate TB in late 2022. Our consensus statements reported the outcomes of the discussion.

2 | METHOD

The consensus conference on prostate TB was held online in November 2022. During this meeting, a group of urologists and imaging specialists with extensive

clinical and academic experience practicing voted on a selection of consensus questions.

Ten key topics were chosen, and a 14-question questionnaire was constructed:

Q1: Should mpMRI be performed before prostate biopsy?

Q2: Will PSMA PET/MRI become a routine exam for initial prostate cancer diagnosis in the future?

Q3: Is prostate targeted biopsy required for patients with mpMRI PI-RADS ≥ 3?

Q4: Which approach of prostate biopsy (transrectal or transperineal) do you recommend first?

Q5: Which diagnostic pathway (combined pathway or MRI pathway) represents the future development direction?

Q6: Is combined systematic biopsy and targeted biopsy necessary for biopsy-naïve patients with suspicious lesions on MRI?

Q7: Is targeted biopsy only sufficient for patients with a prior negative biopsy but suspicious lesions on MRI?

Q8: Does prostate targeted biopsy detect more clinically significant prostate cancer and less clinically insignificant prostate cancer than a systematic biopsy?

Q9: Among the three MRI-guided approaches of prostate targeted biopsies (MRI-TB, FUS-TB, COG-TB), which approach will represent the future development direction?

Q10: How many targeted biopsy cores are needed for clinically significant prostate cancer detection during a prostate targeted biopsy?

Q11: How many cores do you apply in a transperineal systematic biopsy?

Q12: Does the number of systematic biopsy cores need to be reduced in prostate targeted combined with systematic biopsy?

Q13: Can free-hand targeted biopsy replace template targeted biopsy?

Q14: What is the future development of prostate targeted biopsy/prostate diagnosis?

Abbreviations: COG-TB, cognitive MRI/ultrasound targeted biopsy; FUS-TB, MRI/ultrasound fusion targeted biopsy; mpMRI, multiparametric magnetic resonance imaging; MRI-TB, in-bore MRI targeted biopsy; PET/MRI, positron emission tomography/magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting and Data System; PSMA, prostate-specific membrane antigen.

A panel of 25 recognized urologists and 2 radiologists from China was formed. The 27 panelists were asked to vote on each question anonymously based on their understanding or level of agreement. They were suggested to vote "other" and write down their opinion if they did not agree with any given answers. They kept their votes confidential, from each other and the organizers, to express their opinion freely, and to avoid interference, or create a dominant voice.

3 | SELECTION OF IMAGING EXAMINATION OF THE PROSTATE

3.1 | MpMRI in PCa

MpMRI is a major imaging tool for PCa diagnosis and staging. mpMRI has high soft tissue resolution and can anatomically and functionally detect and locate prostate lesions. It has great performance in PCa detection, staging (especially for extracapsular extension), pelvic lymph node (LN), or bone metastasis detection. For an optimal application of mpMRI, the Prostate Imaging Reporting and Data System (PI-RADS) has been developed by an international expert panel[4]. PI-RADS is designed to standardize image acquisition techniques and interpretation of prostate MRI, which is critical for management, communication, multi-institutional research, and clinical trials. The latest version (PI-RADS version 2.1 [PI-RADS v2.1]) published in 2019 had received broad international acceptance among radiologists and urologists and had been widely utilized in daily practice and research[5,6]. According to PI-RADS v2.1, a standard prostate mpMRI protocol should include axial T1WI, multiplanar (axial, coronal, and sagittal) T2-weighted image, axial DWI (with one low *b* value set at 0–100 s/mm^2, one intermediate *b* value set at 800–1000 s/mm^2, and one mandatory high *b* value set ≥1400 s/mm^2), apparent diffusion coefficient (ADC) map and dynamic contrast-enhanced (DCE) images with a temporal resolution of ≤15 s. According to literature reports, mpMRI with PI-RADS scoring had a pooled sensitivity of 0.89 (95% confidence interval [CI]: 0.86–0.92) and specificity of 0.73 (95% CI: 0.60–0.83) for PCa detection[7]. For diagnosing csPCa, mpMRI had a pooled sensitivity and specificity of 0.91 (95% CI: 0.83–0.95) and 0.37 (95% CI: 0.29–0.46)[2]. mpMRI had a high negative predictive value of 0.91 (95% CI: 0.88–0.93) for diagnosing csPCa in biopsy-naïve men[8]. Current guidelines (European Association of Urology, EAU; Chinese Urological Association) strongly recommend mpMRI before prostate biopsies in biopsy-naïve men and men with a prior negative biopsy. However, the role of prostate mpMRI as a triage test (no biopsy for negative mpMRI findings) is still controversial[9].

Several factors, such as magnetic field strength, reception coil type, reporting system, and diagnostic experience of radiologists, may affect the diagnostic efficacy of prostate mpMRI[10]. As 3.0 T MRI had a higher signal-to-noise ratio and imaging quality, it was recommended as a routine modality for prostate mpMRI. An external pelvic phased-array coil instead of an endorectal coil was recommended as the reception coil. PI-RADS v2.1 was recommended as the reporting system for PCa reports. The latest version of PI-RADS has increased the interobserver agreement for PCa detection. The interobserver agreement varied among lesions with

different locations (peripheral zone or transition zone) and different scores. Generally for score ≥3 lesions, the interobserver agreement is good (κ: 0.62–0.78)[11]. To largely reduce subjectivity and improve reproducibility, a dedicated training protocol should be performed in less-experienced readers. Multidisciplinary discussion or uroradiologist discussion could increase the interobserver agreement. Thus, a multidisciplinary meeting is essential before a prostate biopsy[2].

To address the need for MRI protocol simplification and intravenous contrast avoidance, biparametric MRI (bpMRI) of the prostate has emerged. BpMRI uses multiplanar T2-weighted images with diffusion-weighted images (DWIs), which provide high accuracy when localizing the tumor foci in the prostate. Most studies reported a comparable diagnostic efficacy of bpMRI with mpMRI. However, several studies reported the extra value of the DCE sequence in increasing the diagnostic sensitivity for csPCa[12,13]. The key problem is that bpMRI relies on high image quality of DWI sequence, which is a challenge in real clinical practice. DCE sequence may act as a "backup" sequence for prostate lesion evaluation. DCE sequence is also valuable for patients who had prior prostate interventions (transurethral resection of the prostate, benign prostatic hyperplasia therapy, radiotherapy, focal therapy, or embolization) and drug/hormonal therapies that change normal prostate anatomy and signal intensity. MpMRI was preferred in men where the balance between under- and overdiagnosis favors the clinical priority of not missing any csPCa. These patients include those with prior negative biopsies with unexplained raised PSA values, and those in active surveillance who are being evaluated for fast PSA doubling times or changing clinical/pathological status. For men who were highly suspicious of PCa but had prior negative bpMRI examinations, mpMRI is preferred. MpMRI was also recommended in biopsy-naïve men with a strong family history or elevated known genetic risk[2]. Current evidence mostly originates from retrospective data; multicenter prospective clinical trials may provide more evidence for future strategies[11].

Q1: Should mpMRI be performed before prostate biopsy?

Based on the above information on the clinical application of prostate MRI, our panel has voted for the question: 27 (100%) panelists voted for "Yes."

3.2 | Prostate-specific membrane antigen targeted positron emission tomography imaging in PCa

Prostate-specific membrane antigen (PSMA) is a 750-amino acid type II transmembrane glycoprotein that is highly expressed in nearly all primary PCa tissues and LN or bone metastases, with a 100–1000-fold greater expression than that in benign prostatic tissues[14]. Additionally, a positive correlation has been observed between higher PSMA expression and various measures of tumor aggressiveness, including Gleason grade, tumor stage, biochemical recurrence, and castration resistance[15]. Therefore, PSMA is a suitable target for positron emission tomography (PET) imaging in PCa.

Several radiopharmaceuticals (usually urea-based compounds) have been developed to target the extracellular component of PSMA, thereby enabling the rapid accumulation of the tracer in viable PCa cells. Two commonly used groups of PSMA ligands for PET imaging, including ^{68}Ga-coupled PSMA ligands (such as ^{68}Ga-PSMA-11, ^{68}Ga-PSMA-I&T, and ^{68}Ga-PSMA-617) and ^{18}F-coupled ligands (such as ^{18}F-DCFBC, ^{18}F-DCPyl, and ^{18}F-PSMA-1007), have been introduced recently for clinical use[16]. Moreover, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL have been approved by the Food and Drug Administration of the United States[17].

3.2.1 | Local detection of PCa

Precise localization of tumor foci within the prostate gland may help guide biopsy or direct therapies in patients with PCa. PSMA PET has higher sensitivity and better positive predictive value (PPV) and negative predictive value (NPV) than mpMRI. It is also similarly specific for the detection of intermediate- to high-risk primary PCa. The sensitivity, specificity, PPV, and NPV of PSMA PET were 49%, 95%, 85%, and 88%, respectively, and those for mpMRI were 44%, 94%, 81%, and 76%, respectively[18]. For patients with suspected PCa with a total PSA (tPSA) level of 0.4–50 ng/mL, the above-mentioned parameters of PSMA PET were found to be 91.67%, 81.82%, 89.19%, and 85.71%, respectively[19]. In contrast, for patients with a PSA level of 4–20 ng/mL, PSMA PET/computed tomography (CT) outperformed mpMRI in the discrimination of PCa. The sensitivity, specificity, PPV, and NPV of PSMA PET/CT in detecting PCa were 87.88%, 88.24%, 87.88%, and 88.24%, respectively, those of mpMRI were 84.85%, 52.94%, 63.64%, and 78.26%, respectively[20]. However, 5%–10% of primary PCa or PCa lesions showed negative PSMA results on PET. The underlying mechanism of PCa with negative PSMA results on PET remains unclear owing to the lack of prospective studies and correlation with immunohistochemistry.

3.2.2 | Initial staging

Primary staging aims to classify the extent of the main tumor and rule out metastatic spread to the first landing sites, including LNs, bone, and visceral organs. PSMA PET has gained wide acceptance for PCa staging because

of its high efficiency in detecting metastases and identifying recurrent lesions compared with conventional modalities, thereby potentially altering the initial stage, management, and outcomes of PCa. A series of recent studies have revealed the superior diagnostic accuracy of preoperative staging with PSMA PET, with a sensitivity of 38.2%–80%, specificity of 83.3%–100%, PPV of 53.8%–90.9%, and NPV of 67.6%–92.3%[21]. In a recent multicenter randomized clinical trial (ProPSMA study) of 339 untreated patients with high-risk PCa, the diagnostic accuracy of ^{68}Ga-PSMA-11 PET/CT was greater than that of conventional imaging (bone scanning plus diagnostic CT) (92% vs. 65%; $p < 0.0001$)[22].

Compared to conventional imaging, PSMA PET provides more information on regional LN metastases. In most studies, PSMA PET had a sensitivity of 40%–90%, a specificity of >95%, a PPV of 65%–100%, and an NPV of 70%–95% in the detection of LN metastases[21]. In a retrospective analysis of 130 consecutive patients with primary intermediate- to high-risk PCa and subsequent template-based pelvic LN dissection, the sensitivity, specificity, and accuracy of PSMA PET/CT according to the patient-based analysis were 65.9%, 98.9%, and 88.5%, respectively. These values were higher than the conventional imaging values of 43.9%, 85.4%, and 72.3%, respectively, for the detection of LN metastases[23]. However, OSPREY and a recent prospective phase II imaging trial by Hope and colleagues[24] highlighted low sensitivity of ^{18}F-DCFPyL PET/CT and ^{68}Ga-PSMA PET for detecting nodal disease (40.3% and 40.0%, respectively) in patients with newly diagnosed PCa.

For patients with prior radical prostatectomy and pelvic LN dissection (radical prostatectomy+pelvic lymph node dissection), PSMA PET/CT should be performed preoperatively to exclude distant metastases, especially for high-risk patients with potential non-regional LN (M1a) and bone (M1b) metastases undetected by a bone scan. Preoperative staging with ^{68}Ga-PSMA PET/CT appears to allow a more accurate staging of PCa than routine practice in high-risk PCa. The method has been shown to identify several unknown metastatic lesions. PSMA PET/CT exhibited significantly greater sensitivity (96.2% vs. 73.1%) and specificity (99.1% vs. 84.1%) for the detection of metastases[25]. Compared with mpMRI, 27.7% more patients with LN metastases were observed[26]. Pyka and colleagues[24] reported sensitivity and specificity of 98%–99% and 98.9%–100% for ^{68}Ga-PSMA PET and 82.4%–88.6% and 91.6%–97.9% for bone scans, respectively. A prospective single-center phase II imaging study by Sonni et al.[27] found that nearly 43% of providers changed their initial management recommendations for patients with treatment-naïve PCa after using ^{68}Ga-PSMA PET/CT. This technique has helped in identifying patients with oligometastatic disease at initial presentation, with subsequent upstaging of their disease. In patients restaged with advanced or metastatic disease, the locations of extraprostatic disease included pelvic LNs (N1: 36%), distant LNs (M1a: 17%), and bone metastases (M1b: 12%)[21].

3.2.3 | PSMA PET/MRI

Compared to mpMRI, PSMA PET/MRI can more accurately detect primary PCa. Owing to the relatively low spatial resolution of PET, its combination with mpMRI or a hybrid PET/MRI may enhance the classification of a local prostate tumor. A meta-analysis indicated that PSMA PET/MRI had a pooled detection rate of 80.9% at restaging for primary prostate tumors. ^{68}Ga-PSMA PET/MRI detected 98.1% (52/53) of patients with PCa, whereas mpMRI detected only 66.0% (35/53)[28]. The regional sensitivities of PET/MRI and mpMRI were 74% and 50%, respectively, and their specificities were similar (^{68}Ga-PSMA PET/MRI: 88%; mpMRI: 90%)[29]. Compared with PET/CT alone, its combination with mpMRI or PET/MRI significantly improved the sensitivity of detailed lesion analysis from 76% to 89%, especially for lesions classified as PI-RADS score of 3 (net reclassification index: 66.7%; $p < 0.01$)[30]. If PSMA PET/MRI is unavailable, software fusion PSMA PET/MRI is also acceptable compared with PSMA PET/CT or mpMRI alone.

Q2: Will PSMA PET/MRI become a routine exam for initial prostate cancer diagnosis in the future?

17 (63%) panelists voted for “No,” 8 (30%) voted for “Yes,” and 2 (7%) voted for “other.” One illustrated that financial benefits need to be comprehensively considered, while the other proposed that PSMA PET/MRI may be a supplement to mpMRI.

4 | INDICATIONS OF PROSTATE TB

Prostate TB is a method to diagnose the suspected PCa lesions found by various modalities. The clinical value of TB is that it can improve the detection rate of csPCa.

The process of diagnosis of PCa patients is as follows: MpMRI is recommended for patients with PSA > 4 ng/mL, abnormal DRE, and skeletal symptoms who are suspected of PCa. If a positive lesion is found by mpMRI, SB or TB combined with SB will be performed. If the mpMRI result is negative, it is recommended that SB will be performed. The results of mpMRI are very important to decide what types of biopsy are chosen. The sensitivity and specificity of mpMRI for the diagnosis of PCa are 69% and 84%, respectively. PROMIS research shows that if patients are evaluated by mpMRI, a biopsy can be avoided in 27% of patients, the detection of clinically insignificant PCa (ciPCa) can be reduced by 5%, and the detection of csPCa can be increased by 18%. The update of EAU guidelines in 2022 also shows the

importance of mpMRI: Advance mpMRI before the initial biopsy. For patients with a positive mpMRI, TB combined with SB is recommended for the initial biopsy. For patients with a positive mpMRI, only TB is recommended for repeated biopsy. For patients with a negative mpMRI, the first biopsy is jacobinical, while the repeated biopsy is conservative.

The 2019 European Society of Urogenital Radiology (ESUR) prostate MRI guidelines, PI-RADS v2.1 scoring system gives a scoring method for the possibility of csPCa.

The indications of prostate SB are as follows: (1) suspicious nodules of the prostate were found by DRE; (2) suspicious lesions were found by prostate MRI or CT; (3) serum tPSA > 10 ng/mL; (4) PSA density (PSAD) was > 0.15 ng/mL^2 and/or PSA velocity (PSAV) > 0.75 ng/(mL year); (5) the results of other prostate tumor markers were abnormal, such as PCa antigen 3; (6) diagnosis of PCa with metastatic disease.

Generally, prostate TB is recommended for patients with a PI-RADS score of 4 or 5. Does a patient with a PI-RADS score of 3 need a biopsy? At present, there is no definite tendentious diagnosis of lesions with PI-RADS scores of 3, which leads to huge differences in practice mode (from conservative treatment, imaging follow-up to surgical treatment), cost, and potential clinical outcomes among different institutions. The advantage of active monitoring is avoiding the burden and risk caused by biopsy, but it may lead to missing or delaying the diagnosis of some csPCa lesions, which will have irreversible consequences for patients. Whether intervention measures should be taken for this kind of lesion is still controversial, and the proportion of csPCa is small but should not be ignored. Studies have shown that the diagnostic rate of csPCa in lesions with a PI-RADS score of 3 ranges from 5% to 30%, and the final detection rate of csPCa is relatively low[31]. Therefore, some clinicians suggested that patients with a PI-RADS score of 3 should undergo an MRI follow-up instead of an immediate biopsy.

The incidence of a PIRADS score of 3 and the detection rate of csPCa in this category depends on the incidence of PCa in the population, quality of mpMRI, professional knowledge of radiologists, and methods used to verify the biopsy results. Reviewing mpMRI by senior experts can reduce the incidence of PIRADS 3, as well as the proportion of PIRADS 3 from 20% to 6%. The further improvement of the mpMRI standard can identify csPCa patients with a PI-RADS score of 3, and the specific method is to use contrast agent enhancement mode or refer to ADC value, PSAD, and other serum biomarkers. Therefore, it is of great clinical significance to classify the lesions with a PI-RADS score of 3 in more detail and screen out the patients who need to be biopsied. For example, if the patient's DRE or PSA is abnormal, a PI-RADS score of 3 should be regarded as positive, requiring peer review and biopsy. Patients who have not received prostate biopsy in the past and PI-RADS ≥ 3 need to receive combined SB and TB. For patients with negative SB results in the past, only MRI TB is required. When TB is performed, multineedle biopsy pathology (local saturation) should be obtained from the target defined by MRI, so as to minimize the diagnosis deficiency and improve the risk stratification of the tumor. It has been reported that with the help of artificial intelligence algorithms, imageology can extract quantitative parameters from conventional medical images, construct predictive models, and provide additional information for making individualized diagnoses and treatment plans.

Therefore, we suggest that when PSA > 4 ng/mL, PI-RADS scores of 3, it is necessary to refer to other indicators to help judge whether TB is needed, such as (1) age > 70 years old[32]; (2) DRE positive; (3) prostate volume < 36 mL; (4) PSAD > 0.15 ng/mL^2[32]; (5) ADC value of mpMRI < 900 mm^2/s[33]; (6) imaging omics prediction model[34].

Q3: Is prostate targeted biopsy required for patients with mpMRI PI-RADS ≥ 3?

16 (59%) panelists voted for "Yes," 2 (7%) voted for "No," and 9 (33%) voted for "other." One panelist proposed that TB is necessary for patients with mpMRI PI-RADS > 3, and the other illustrated that we should decide based on PSA, family history, PSMA PET/CT, prostate health index, and so on.

5 | COMPARISON OF TRANSPERINEAL AND TRANSRECTAL PROSTATE BIOPSY

As a gold standard for PCa diagnosis, prostate biopsy has emerged as one of the most frequently performed urologic procedures. Nowadays, biopsy techniques are much more advanced, ranging from palpation- to image-guided transrectal (TR) biopsy to transperineal (TP) biopsy.

The ultrasound-guided TR biopsy can be performed in an outpatient clinic without anesthesia. In contrast, the TP approach is performed under general anesthesia or local anesthesia and requires an extra template grid for biopsy guidance. Therefore, TR biopsy is considered to be more cost and time effective in some countries and is widely used for SB. TP biopsy is reserved as an alternative approach for TR biopsy-negative patients and anterior and/or apical sampling. However, according to Murat Yavuz Koparal's study, although the mean overall cost (biopsy and re-presentations) was higher in the TP group, it reduced over time and was similar for patients who re-presented[35]. Furthermore, the debate comparing the different detection rates and complications of the biopsy methods remains controversial.

Most research showed that the PCa detection rate is similar between the TP and TR biopsy[36–38]. Even

through image-guided TB, the detection of any PCa or csPCa is still similar[39]. However, some research showed that TP biopsy had a higher detection rate of csPCa than TR biopsy for all patients[40]. A prospective study carried out by Pietro Pepe et al.[41] showed that mpMRI/TR ultrasound (TRUS) cognitive targeted TP biopsy could find a greater percentage of csPCa in the anterior zone, compared with the TR approach. Therefore, the TP approach is preferred in patients with anterior and apical lesions due to its superiority in detecting csPCa[42].

Severe complications of prostate biopsy are rare, whereas minor complications like hematuria and hematospermia are relatively frequent and almost always self-limiting in both TR and TP biopsy[43]. The rectal bleeding rate is about 17%–27% after a TR biopsy, while it is extremely rare after a TP biopsy[44,45]. With a growing population of life-long use of anticoagulation agents, the management of these agents has become a major issue in the perioperative period of a prostate biopsy. Due to its less risk of severe rectal bleeding, TP biopsy could be more suitable for patients with anticoagulation agents than TR biopsy. The infectious complications rate and readmission rate for sepsis are higher after TR biopsy, compared to TP biopsy. The urinary retention rates have been reported differently in different research. Overall, in terms of urinary retention, TR biopsy is better than TP biopsy[35–37,46].

There is slightly more intraprocedural pain in TP biopsy than in TR biopsy transiently. However, they have a similar effect on temporary health-related quality of life[47].

Q4: Which approach of prostate biopsy (transrectal or transperineal) do you recommend first?

24 (89%) panelists voted for TP biopsy, and 3 (11%) voted for TR biopsy.

6 | PROSTATE TB PATHWAYS

An MRI-TB can be used in two different diagnostic pathways: (1) the "combined pathway," in which patients with a positive MRI undergo combined systematic and TB, and patients with a negative MRI undergo SB only; (2) the "MRI pathway," in which patients with a positive MRI undergo MRI-TB only, and patients with a negative MRI received no biopsy at all[2]. The PRECISION trial[48] first introduced the "MRI pathway," in which 500 biopsy-naïve patients were randomized to receive either MRI with/without MRI-TB (252 patients, TB for patients with positive MRI and no biopsy for patients with negative MRI) or TRUS-guided 10-to-12-core SB (248 patients, no prebiopsy MRI). CsPCa (Gleason score ≥3 + 4) was detected in 95 men (38%) in the MRI pathway group compared with 64 men (25.8%) in the SB group. Meanwhile, fewer patients received a diagnosis of non-csPCa in the MRI pathway group than that in the standard-biopsy group (23/252, 9% vs. 55/248, 22%). The "MRI pathway" is appealing since it could decrease the number of biopsy procedures and reduce the detection of low-grade cancer. However, omitting SB would also increase the risk of missing cancer of high grade. Thus, the added value of SB for patients with positive or negative MRI should also be taken into consideration separately.

For biopsy-naïve patients with a positive prebiopsy MRI, the added value of SB has been explored previously. An MRI-FIRST trial[49] enrolled 251 biopsy-naïve patients who had been referred for prostate MRI before biopsies, of whom 198 patients had positive MRIs (Likert ≥3) and received MRI-TB combined with SB. CsPCa was detected in 94 (37%) out of 251 patients, with 13 (14%) of these 94 patients diagnosed by SB only, 19 (20%) by MRI-TB only, and 62 (66%) by both techniques. Detection of csPCa by SB only (29.9%) and MRI-TB only (32.3%) did not differ significantly. However, csPCa would have been missed in 5.2% of patients whose SB had not been done, and in 7.6% of patients whose MRI-TB had not been done. Using the combined biopsy as the reference for patients with positive MRIs and omitting SB would miss 14% (13/94) of all detected ISUP grade ≥2 cancer. In another case, a 4M trial[50] included 317 biopsy-naïve patients with positive MRI results (PIRADS 3–5) and arranged MRI-TB followed by SB. An additional 7% (21/317) of csPCa cases were detected using the SB only. Using the combined biopsy results as the reference for patients with a positive MRI and omitting SB would miss 12% (21/180) of all detected csPCa. In a pooled data of 15 reports on the added value of SB, omitting SB for patients with positive MRI resulted in a 12.81% decrease in the detection of csPCa and 20.76% decrease in non-csPCa[51]. In 2020, Ahdoot et al.[52] retrospectively enrolled 2103 men (mixed patients with biopsy-naïve and prior-negative biopsy) who underwent MRI-TB and SB concurrently. The combined biopsy led to cancer diagnoses in 208 more men (9.9%) than that with either method alone. Using the combined biopsy as the reference, omitting SB would miss 13% (123/918) of all detected csPCa. In the repeat-biopsy setting, the subgroup of 152 patients in the FUTURE trial[53] who underwent both MRI-TB and SB indicated that MRI-TB detected more ISUP grade ≥2 cancers than SB (34% vs. 16%), and only 3.8% (2/53) of all detected csPCa would have been missed if SB had been omitted. Data from the Cochrane meta-analysis also indicated that the pooled absolute added value of SB was only 2.7% (1.2%–5.7%) in men with a previous negative biopsy[54].

For patients with a negative prebiopsy MRI, data from the Cochrane meta-analysis indicated that the pooled proportions of negative MRI were 33.0% (25.6%–41.3%) in the biopsy-naïve setting and were equivalent in the prior-negative biopsy setting. For biopsy-naïve men with a negative MRI, SB detected

8.1% (5.6%–11.6%) additional csPCa and 18.4% (14.2%–23.7%) additional men with non-csPCa[54]. Combining other applicable parameters, such as PSAD may help refine the risk of csPCa. In a meta-analysis of eight studies, pooled NPV for csPCa was 84.4% (95% CI: 81.3%–87.2%) in the whole cohort, 82.7% (95% CI: 80.5%–84.7%) in biopsy-naïve men, and 88.2% (95% CI: 85%–91.1%) in men with prior negative biopsies. In the subgroup of patients with PSAD < 0.15 ng/mL^2, NPV increased to 90.4% (95% CI: 86.8%–93.4%), 88.7% (95% CI: 83.1%–93.3%), and 94.1% (95% CI: 90.9%–96.6%), respectively[55]. In a recent single-center study in which 240 biopsy-naïve men with negative MRI (PI-RADS 1–2) were retrospectively recruited, simply omitting SB would have missed 39 (16.3%) PCa patients and 22 (9.2%) csPCa patients, while combining a negative MRI with a PSAD below 0.20 ng/mL^2 significantly increased the NPV in excluding PCa (91.0%) or csPCa (100%)[56]. Taking the above into consideration, the use of PSAD remains currently limited due to the lack of standardization of prostate volume measurement, as well as variations in regional cancer prevalence.

Q5: Which diagnostic pathway (combined pathway or MRI pathway) represents the future development direction?

25 (93%) panelists voted for the "combined pathway," and 2 (7%) voted for the "MRI pathway."

Q6: Is combined systematic biopsy and targeted biopsy necessary for biopsy-naïve patients with suspicious lesions on MRI?

All panelists (100%) agreed that combined SB and TB are necessary for biopsy-naïve patients with suspicious lesions on the prebiopsy MRI.

Q7: Is targeted biopsy only sufficient for patients with a prior negative biopsy but suspicious lesions on MRI?

For patients with a prior negative biopsy but have suspicious lesions on MRI, 8 (30%) panelists voted for "Yes," 14 (52%) panelists voted for "No," and 5 (18%) voted for "other," depending on the specific conditions of previous biopsies.

7 | TB AND SB

The strategy for prostate biopsy in men with elevated PSA levels, abnormal DRE, and suspicious lesions on mpMRI is shifting to MRI-TB worldwide, but the optimal biopsy paradigm is debated due to the systematic TRUS biopsy with substantial evidence as a supplement. All urologists, clinicians, and patients are expected to exercise the optimal biopsy strategies without a near 0% missing or underestimate diagnosis of csPCa, and simultaneously a low detection rate of ciPCa. According to the previous clinical trials, prospectively or retrospectively, and systematic review or series of meta-analysis[48,52,57–59], the majority of panelists supported that MRI-TB could improve the detection rate of csPCa and reduce the detection rate of ciPCa. In most regions worldwide, patients with suspected PCa have typically undergone SBs of the prostate. However, in high-volume tertiary referral centers, MRI-TB has often been used to detect PCa.

In recent years, bpMRI or mpMRI is a routine examination for patients with suspected PCa before prostate biopsy. The PROMIS trial[60] showed mpMRI with a significantly high sensitivity (88%) for PCa of ISUP 2 or more and an NPV of 76%. A meta-analysis on PI-RADS v2 also showed that the sensitivity of mpMRI was up to 90% for detecting csPCa[7,8] and the NPV of mpMRI was up to 95%[8,61]. Prebiopsy mpMRI improves the accurate location and sensitivity of suspicious lesions of csPCa, and PI-RADS v2 provides a good reference for urologists and radiologists to access the targeted lesion.

In a pooled data of 14 studies analyzing the agreement between TB (any technique) and SB separately in the same biopsy session, overall PCa detection rates between TB and SB with a relative sensitivity 0.98 (95% CI: 0.9–1.07) were not significantly different[57]. However, TB improves the detection rates of csPCa compared to SB, with a relative sensitivity of 1.16 (95% CI: 1.02–1.32)[57]. In addition, the pooled estimates of detection rates demonstrate that TB dramatically reduces ciPCa compared with SB with a relative of 0.47 (95% CI: 0.35–0.63)[57]. In the subgroup analyses of a meta-analysis exclusively based on randomized controlled trials (RCTs), providing the highest level of evidence, a seemingly more evidence-based view was that TB detected significantly more csPCa than SB both in primary biopsy patients and in repeated biopsy patients (pooled relative detection rates of 1.42 [95% CI: 1.02–1.98] and 1.60 [95% CI: 1.01–2.54], respectively)[62]. However, there is no significant difference in ciPCa detection rates for TB and SB with a pooled relative detection rate of 0.89 (95% CI: 0.49–1.62)[62]. When TB and SB were performed in the same population, a possible bias could not be omitted that realizing the location of the MRI suspicious lesions could have influenced the random sampling in SB. To exclude this bias, participants of the PRECISION trials[48] were randomized into either the TB group or the SB group. It has been shown that TB improved the detection rates of PCa of ISUP grade ≧2 (38%) than that of SB (26%) ($p = 0.005$, detection ratio 1.46). The biopsy-naïve patients with an elevated risk of PCa from another RCT cohort[63] were randomized into the prebiopsy mpMRI group (group A, TB for patients with MRI visible-lesion and SB for patients with MRI invisible lesion) and an SB group (group B). This demonstrated that the overall detection rates of csPCa were significantly different between groups A and B (43.9% vs. 18.1%, respectively; $p < 0.001$).

Nonetheless, we must face the truth that mpMRI can identify neither all PCa nor all csPCa cases, and TB could also miss some csPCa. An updated systematic

review revealed that TB plus SB improved csPCa detection rates by 5% ($p = 0.0005$, 95% CI: 2%–8%) compared with TB alone[64]. Another meta-analysis demonstrates that men who have negative or nonsuspicious mpMRI with PIRADS 1–2 have an approximately 10% probability of harboring csPCa of ISUP 2 or more[8]. An RCT study of a small sample[65] revealed that the cancer detection rate in men with MRI invisible lesions was up to 23%. In addition, csPCa detection by TB highly depends on the quality of mpMRI, readers' interpretation of PI-RADS, and target sample experience. These biases vary even with different academic medical centers and clinicians.

To sum up, combining targeted and SB has gained wide acceptance in the present clinical practice due to its satisfactory performance in detecting csPCa and PCa.

Q8: Does prostate targeted biopsy detect more clinically significant prostate cancer and less clinically insignificant prostate cancer than a systematic biopsy?

23 (85.2%) panelists voted for TB with a higher detection rate of csPCa and a lower detection rate of ciPCa than that of SB, and only 4 (14.8%) voted for the opposite opinion.

8 | THREE TECHNIQUES OF TB

The main clinical TB methods include in-bore MRI-TB, MRI/ultrasound fusion TB (FUS-TB), and cognitive MRI/ultrasound TB (COG-TB).

MRI-TB has the highest level of hardware requirements, including positioning devices, special biopsy needles that require demagnetization, and software for guidance. This technique is completely guided by MRI, making the accuracy the highest theoretically with less operator's experience required. For the lesions identified by MRI, only two biopsy cores are needed, which are of high accuracy and have little trauma. It can be performed under local anesthesia infiltration. The disadvantage of MRI-TB is that the SB cannot be performed in one session. Therefore, it is mainly used for patients with definite MRI lesions. This procedure requires MRI prescanning and repeated positioning; thus, preparation will take 20–30 min despite the short operation time. This approach requires that the patient can remain in a prone position awake for long periods of time stably. Moreover, the biopsy can only be performed via the rectum wall with complete rectal disinfection (including abrosia, oral antibiotics, laxatives, and betadine enemas).

COG-TB does not require additional software guidance and relies solely on the operator's understanding of MRI and the comparison of ultrasonic images. Therefore, COG-TB has the lowest level of equipment requirements, but a relatively high level of the operator's image reading ability and targeting proficiency by ultrasound. This makes COG-TB more suitable to launch at hospitals and clinics without software, but operators must receive standardized systematic training, including urology and imaging knowledge training.

The FUS-TB is in between, requiring certain hardware and software support. Still, there are variations among different software and differences in positioning and operation. Improvements in software positioning accuracy are always in need of further exploration. The FUS-TB system often requires a dedicated ultrasound device, a system equipped with fusion software, a positioning probe, and, in some cases, a special positioning rack and guide grid. This increases the cost of the piercing system. Moreover, the FUS-TB can also perform free-hand biopsy for hard-to-penetrate sites, such as the lesions behind the pubic bone. Both FUS-TB and COG-TB can perform TB and SB in one operation, and the overall risk of infection is low.

One meta-analysis[57] compared the differences in the overall PCa detection rates and csPCa detection rates among these three techniques. The initial search identified 2562 studies and 43 were included in the meta-analysis. Out of these studies, 11 used MRI-TB, 17 used FUS-TB, 11 used COG-TB, and 4 used a combination of techniques. In 34 studies, concurrent TRUS-GB was performed. They found no significant difference between MRI-GB (all techniques combined) and TRUS-GB in terms of the overall PCa detection (relative risk, RR: 0.97 [0.90–1.07]). MRI-GB had higher detection rates of csPCa than TRUS-GB (RR: 1.16 [1.02–1.32]), and a lower yield of ciPCa (RR: 0.47 [0.35–0.63]). There was a significant advantage ($p = 0.02$) of MRI-TB compared to COG-TB in overall PCa detection and no difference between MRI-TB compared to FUS-TB ($p = 0.13$), as well as between FUS-TB and COG-TB ($p = 0.11$). For csPCa detection, there were no significant differences among these techniques.

An RCT trial[58] compared the detection rates of these three TB techniques in patients with a previous negative SB and suspicion of PCa on the MRI. The result shows no significant differences in the overall PCa detection rates (FUS-TB 49%, COG-TB 44%, MRI-TB 55%; $p = 0.4$), as well as detection rates of csPCa (FUS-TB 34%, COG-TB 33%, MRI-TB 33%; $p > 0.9$).

Therefore, no significant differences were observed among the three types of TB of PCa or csPCa detection rate both for the initial biopsy or repeated biopsy cohort.

Q9: Among the three MRI-guided approaches of prostate targeted biopsies (MRI-TB, FUS-TB, COG-TB), which approach will represent the future development direction?

2 (7%) panelists voted for MRI-TB, 12 (44%) voted for FUS-TB, and 13 (48%) voted for COG-TB. The majority of panelists (48%) believe COG-TB is more in line with the domestic medical situation and relatively easier to expand. COG-TB can better meet complex clinical needs since it does not require extra hardware and has higher

freedom of operation. Another 44% of panelists believe that FUS-TB is more standardized than COG-TB and could form a relatively uniform TB mode. 2 panelists suggested that MRI-TB will be widely used in clinical practice as it has technical advances. However, it is currently only applicable in specific hospitals.

9 | NUMBER OF CORES NEEDED FOR ONE LESION

International guidelines recommend TB over other methods due to its higher detection rate of csPCa, making it widely used in clinical practice. However, the protocol for MRI TB is variable, and the reported number of cores per lesion range from 1 to 9[59]. To reduce overdiagnosis, overtreatment, and complications, identifying the optimal number of cores is necessary.

The recommended number of cores per lesion varies in different guidelines. The EAU-EANM-ESTRO-ESUR-SIOG guidelines suggest that at least four cores should be taken per lesion[2]. The PI-RADS Steering Committee divided TB into MRDB (MRI-directed biopsy with two to four cores per lesion) and MRDB focal saturation (four or more cores per lesion, including surrounding sextants)[66]. MRDB is recommended for a PI-RADS score over 3 and MRDB focal saturation is mainly recommended for a PI-RADS score of 4–5[66]. The American Urological Association (AUA) and Society of Abdominal Radiology guideline suggested that at least two cores should be obtained[67]. Current international guidelines show bifurcation on the optimal number of cores and some studies tried to settle the differences.

Recent studies showed that three TB cores per lesion may be suitable. Song et al.[68] illustrated in a prospective cohort that three-core TB have a consistent csPCa detection rate compared with four or more cores as only three lesions with csPCa were missed (3/101). Tu et al.[69] pooled five studies and showed that three-core TB detected 91.6% of csPCa, and the value of the fourth and fifth cores is limited. Beetz et al.[70] and Seyfried et al.[71] also demonstrated that three cores can detect most csPCa and optimize histopathologic diagnosis. Differently, Dimitroulis et al.[72] proposed that one core could be sufficient as the second core shows little improvement. Ploussard et al.[77] suggested that at least four cores are needed in lesions with PI-RADS score of 3, and three cores are needed in PIRADS 4–5. Most studies support that three TB cores per lesion can effectively detect most csPCa, but more evidence is needed. Additionally, these studies used different biopsy techniques, which may influence the csPCa detection rate.

Biopsy techniques can be divided into techniques guiding the biopsy and core sites. Three techniques guiding the biopsy show slight differences in detection rate. MRI/US fusion is used in three studies and three-core TB can detect 90% of patients with csPCa[68,69,73]. The three-core TB using cognitive fusion compared to the one-and five-core TB showed an change in csPCa detection rate by +6.4% and –2.4%[74]. The three-core TB using MRI in-bore can also detect all csPCa[71]. Based on these studies, the value of the fourth and fifth biopsy cores may be limited regardless of the biopsy guiding techniques. Cores sites can be divided into two patterns: getting samples along the long axis[75] or from the central and peripheral parts[68,70,73]. The center cores are the most valuable[75,76]. However, no studies have compared these two patterns. In conclusion, whether different amounts of cores should be applied to different biopsy techniques is still unclear.

The condition of the patient may also influence the optimal number of cores. A higher PI-RADS suggests a higher risk of csPCa[59,70]. A nonparametric Bayes classifier trained with PI-RADS score, PSAD, lesion size, zone, and location can help to evaluate the value of the first biopsy core, but these factors have no independent predictive power[70]. A model to predict the optimal number of cores has not been proposed; thus, urologists and clinicians adjust the number of TB cores mainly based on subjective judgment[68,73].

Q10: How many targeted biopsy cores are needed for clinically significant prostate cancer detection during a prostate targeted biopsy?

16 (59%) panelists voted for three cores, 5 (19%) voted for two cores, 3 (11%) voted for more than four cores, 2 (7%) voted for four cores, 3 (11%) voted for five or more cores, and 1 (4%) voted for “other” with two to four cores.

10 | THE CORE NUMBER FOR SB OF PROSTATE

SB is the “gold standard” for the diagnosis of PCa. How to improve the detection rate of csPCa and avoid the detection of ciPCa is of great importance for PCa diagnosis[49]. The six-core method was initially used in the systematic approach, while it is rarely used currently due to the low detection rate of positive cores[78]. Saturation biopsy with >20 cores would increase the detection rate of PCa. However, the high incidence of complications should not be ignored. The method of at least 10–13-core SB, for example, 12 cores in four areas or 13 cores in five areas, has been developed and accepted to increase the rate of positive cores with a relatively low incidence of complications. However, there is still no consensus on the optimal number of SB cores following TB. Prostate volume is a crucial consideration. In patients with <30 mL prostate volume, the detection rate of the 14-core scheme was similar to the eight-peripheral cores protocol. In patients with a 30–50 mL prostate volume, a 12-core peripheral biopsy reproduced the results of the 14-core sampling. In

prostates larger than 50 mL, an even more extensive procedure was mandatory, considering the low detection rate of the 14-core scheme[79]. The biopsy cores could be appropriately increased in patients with large volumes of the prostate, especially the apex and ventrolateral aspects. If the prostate volume is small, the number of biopsy cores could also be appropriately reduced to avoid injuring adjacent tissues and reduce complications. However, a minimum of eight cores should be guaranteed. In a retrospective study, the total detection rates of PCa and csPCa were similar between the 12- and 10-core prostate biopsy strategies. There were no statistically significant differences in the detection rates of PCa and csPCa between the 12-core method and any other method in patients with a PSA ≥ 20 ng/mL. However, the detection rate of csPCa differs significantly from other methods except for the 10-core biopsy method in those with a PSA < 20 ng/mL The 12-core biopsy method was statistically different from the eight-core, modified six-core, and standard six-core methods except for the 10-core method for the PCa and csPCa detection rates regardless of age <70 years or ≥70 years[80]. Hence, a precise subgroup analysis is necessary to optimize the minimal biopsy cores.

TB combined with SB was strongly recommended in biopsy-naïve patients with MRI-visible lesions, with an increased detection rate of ISUP grade > 2 and grade > 3 PCa by approximately 20% and 30%[52]. However, the number of SB cores in the TB combined with SB remains uncertain. Song and colleagues[81] conducted a prospective study and found that MRI/FUS-TB followed by SB of the nontargeted sector with fewer SB cores has the same PCa and csPCa detection rates compared with standard TB plus SB. Freifeld et al.[82] demonstrated that MRI-based TB plus six-core ipsilateral SB may increase the detection of csPCa and reduce the overdiagnosis of indolent cancers compared with TB alone or TB plus contralateral six-core SB. Shen et al.[83] showed that the MRI/ultrasound TB plus six-core lateral SB had the highest detection rate of PCa or csPCa and a lowest missed diagnosis rate compared with TB alone, 12-core SB alone, TB plus ipsilateral six-core SB, or TB plus contralateral six-core SB. Hagens et al.[84] revealed that MRI-directed SB plus perilesional SB could detect 96.8% of csPCa cases and reduce the detection rate of nsPCa by 12.8%, with a significant reduction of 5.2 biopsy cores per patient on average, compared with standard TB plus SB. Hansen et al.[85] showed that 10–20-core saturation TB detected 7–10 Gleason score PCa by more than 25% compared to a two-core TB approach and as many men (91%) as the 20–26-core TB combined with SB. In summary, the number of SB cores in the TB plus SB might be reduced in carefully selected patients using a specific biopsy approach. Further research is still needed to determine whether the number of SB cores needs to be reduced in prostate TB plus SB in the future.

Q11: How many cores do you apply in a transperineal systematic biopsy?

13 (48%) panelists voted for at least 10–12 cores and increasing cores according to prostate volume, 10 (37%) voted for 10–12 cores, 3 (11%) voted for more than 12 cores, and 1 (4%) voted for "other."

Q12: Does the number of systematic biopsy cores need to be reduced in prostate targeted combined with systematic biopsy?

14 (52%) panelists voted for "Yes," 12 (44%) panelists voted for "No," and 1 (4%) voted for "other" with an illustration that further stratification and research are needed.

11 | FREE-HAND TB

To date, no RCT has compared free-hand TB to template TB. Zhang et al.[86] compared free-hand TP mpMRI/TRUS fusion TB to SB and found that the former could detect more csPCa with fewer cores. Other studies[87–89] reported that free-hand targeted combined SB under local anesthesia had good tolerability, few complications, and a high csPCa detection rate. The free-hand biopsy is becoming increasingly popular, but 30% of team members still believe that free-hand TB cannot replace template TB, and the reasons for this can be gleaned from the responses of the other two panelists who chose "others." One panelist believed that the choice to perform biopsy free-hand or using a template should be based on the surgeon's habits, equipment, and purpose of post-biopsy treatment, while another panelist believed that a skilled surgeon could replace the template TB for a free-hand TB. Template TB requires the corresponding TP prostate biopsy positioning template, other brachytherapy stepping units and grids, and sophisticated ultrasound and biplanar ultrasound probes, which are not available at all medical institutions. The surgeon's previous biopsy experience affects the selection of the type of targeted biopsies. In addition, whether or not undergoing radical prostatectomy or focal therapy after a biopsy can also influence the surgeon's choice. The research by Lee et al.[90] showed that reducing the number of systematic cores during TB would impact the treatment plans for the biopsy, more lesions can be identified through a more intensive SB, and a more accurate template plan for focal therapy can be developed. The advantage of template biopsy is providing a more intensive and systematic prostate biopsy planning. Therefore, it cannot be replaced by a free-hand biopsy.

Free-hand TB is a cheaper, faster, and more accessible procedure. Free-hand biopsy requires less equipment, but more experience of the surgeon[91].

Free-hand TB does not require general anesthesia, requires less resources, and has a shorter operation time than template TB. There are two approaches to

free-hand biopsy, a pure freehand or a probe-mounted needle guide technique. The earlier free-hand biopsy adopted the fan technique. A 22-gauge spinal needle was inserted transperineally on each side approximately 1.5 cm above the rectum on a 45° line from the median[92]. Through the same hole, an 18-gauge needle was inserted and all cores of the peripheral prostate area were obtained using the fan technique[92].

A study reported no significant difference in the total PCa detection rates between free-hand TB and template TB in the patients with PSA < 20 ng/mL, but for the detection rate of cancer with Gleason score ≥7, the template TB group was significantly higher than the free-hand TB group, especially in patients with PSA < 10 ng/mL. For the anterior prostate zone, the detection rate of the template TB group was higher than the free-hand targeted group.

It seems that free-hand biopsy is becoming increasingly popular, but template TB still demonstrates superiority.

The significance of TB is that it has the ability to diagnose more csPCa with fewer biopsy cores, which is the advantage of free-hand TB.

Q13: Can free-hand targeted biopsy replace template targeted biopsy?

17 (63%) panelists voted for that it could, 8 (30%) voted for that free-hand TB could not replace template TB, while 2 (7%) chose "other." This issue remains controversial.

12 | THE FUTURE DEVELOPMENT OF TB/PROSTATE DIAGNOSIS

Suspected PCa is traditionally diagnosed using PSA screening and ultrasound-guided standardized SB. Multiple biopsies are unnecessary, especially for ciPCa[93]. Recently, many studies have shed light on the high sensitivity of mpMRI in the diagnosis of PCa. In 2019, the EAU and AUA updated their guidelines and recommended mpMRI before biopsy and TB with SB together for biopsy-naïve patients with suspicious findings on the mpMRI[54,94]. The necessity of biopsy for mpMRI-negative patients remains controversial since the PROMIS trial reported that 24% of patients with negative findings on mpMRI had csPCa. Meanwhile, 49% (205/418) of patients with a suspicious cancerous lesion, who were negative for cancer on the template prostate mapping biopsy, were reported to have undergone unnecessary biopsies[60]. Limitations of the mpMRI imaging modality warrant the identification of additional biomarkers and image modalities.

PSMA is a membrane protein that is significantly overexpressed in PCa cells[95]. It has been shown that PSMA PET-guided fusion biopsy can differentiate men with csPCa from those with a negative mpMRI or biopsy. Lopci et al.[96] selected 25 patients with positive findings on ^{68}Ga-PSMA-11 PET/CT who subsequently underwent PET/CT-guided fusion biopsy. While PSMA PET/CT was positive in 25 patients, only 11 patients were pathologically confirmed with PCa.

A prospective randomized study revealed that PSMA PET/CT detected significantly more cases of csPCa in patients with PSA 4.0–20.0 ng/mL than TRUS (27.02% vs. 8.82%), and PSMA PET/CT-guided TB also detected significantly more PCa and csPCa with fewer complications than TRUS-GB[97]. Liu et al.[98] introduced the molecular-imaging-for-PSMA expression score criteria to explore the role of ^{68}Ga-PSMA PET/CT-guided TB in the detection of csPCa. They found that the number of cores was significantly lower with TB than with SB when cancer detection rates were similar. The median cores of PSMA PET/CT-guided TB and SB were 2 and 12, respectively. PSMA PET/CT-guided TB had a better detection rate of csPCa and a significantly decreased biopsy core.

PSMA PET/MRI combines mpMRI data acquisition with the molecular imaging approach using PSMA as a specific and sensitive ligand for the detection of PCa. PET/MRI is superior to PET/CT because of the higher soft tissue contrast afforded by mpMRI techniques. This counterbalances the technological limitation between the two modalities. PSMA PET/MRI has a higher sensitivity than either method alone. Matthias and colleagues[28] reported that the sensitivity and specificity of PSMA PET/MRI were 76% and 97%, respectively. In a pilot study, PSMA PET/MRI demonstrated promising results in PPV and specificity for the diagnosis of PCa, and verified the feasibility of its guided FUS-TB[99]. Dr. Niu found that patients who scored 3 or 4 (scoring system based on PSMA PET/MRI) on PSMA PET/MRI may only undergo TB in the future. With further study, patients who scored 1 could avoid the unnecessary biopsy even with a rising PSA[100].

Despite the advantage of PSMA PET/MRI in PCa diagnosis, caution must still be taken during use since this high-precision equipment is expensive to purchase and maintain. Its expenses are costly for most hospitals and even the top institutions. Second, the high cost of examination may not be covered by medical insurance programs. Third, the drug that PSMA uses is not available in most hospitals. How and when to use this promising technique still needs further study.

PSMA PET/CT combined with mpMRI could be used in place of PSMA PET/MRI for selected patients. PSMA PET/CT used at the right time could help patients avoid unnecessary biopsies. Using the PI-RADs v2.1 system when PI-ADS ≤ 3, the cancer detection rate is rare but complications, including bleeding, hematuresis, infection, and pain, often occur[101]. Also, the cost of the unnecessary biopsy and unexpected hospitalization will increase the financial burden on patients. If the PSMA PET/CT result is negative, patients could avoid the biopsy regardless of the level of PSA. When PI-RADS > 3,

the cancer detection rate is relatively high, PSMA PET/CT could be used to distinguish the cancerous patients and provide a more accurate clinical stage. Patients with both positive results on the two imaging modalities are all confirmed as PCa in some cohorts, thus radical prostatectomy is performed without biopsy in these selected patients[102]. Further research is being conducted.

Niu's study found that the location of the index tumor (IT) on the RP specimens showed 100% accuracy with the suspicious tumor visible on PSMA PET/MRI. It seems that patients who scored 3 or 4 on PSMA PET/MRI may only undergo TB in the future with further study[100]. Accurate detection of IT is very helpful for clinical decision-making. The PSMA PET/MRI-guided fusion TB is verified safe and feasible. An operator could outline the cancerous lesions according to both the parameters from mpMRI, such as DWI, ADC, T2-weighted fast spin echo, and expression of PSMA. However, whether the PSMA PET/MRI-guided fusion TB alone could replace SB still needs further investigation. It is also important to pay attention to its tumor detection, as well as factors that may affect the operation strategy, such as the protection of neurovascular bundles and patients' prognosis.

In conclusion, PSMA PET/MRI and its guided FUS-TB are promising techniques, but their wide use should still be verified by further research. PSMA PET/CT could be advised at the right time for selected patients as its high specificity could overcome the disadvantages of mpMRI. Some patients could benefit from it to avoid unnecessary biopsy.

Q14: What is the future development of prostate targeted biopsy/prostate diagnosis?

As various techniques develop, prostate biopsies will be more automatic, digitized, accurate, and artificially intelligent in the future. Some experts believe in the future use of PSMA PET in the diagnosis of PCa, especially in perplexing cases. Also, experts believe that as imaging techniques and surgical skills progress, more accurate preoperative diagnosis and fewer postoperative complications will make biopsy-free possible in the future. Other experts emphasize the potential applications of radiomics and artificial intelligence and their roles in future biopsies. Robots have been widely used in various fields of medicine, including in biopsy. Many teams are researching, preparing, or working on machine-assisted biopsy. In the near future, it is possible for these devices to be used at clinics to improve biopsy accuracies.

13 | SUMMARY

The Panjiayuan consensus summarizes the current important issues of prostate TB, based on a thorough analysis of existing studies and practice status, and a full discussion. According to the voting results of the experts, we reached the following consensus:

- MpMRI should be performed before prostate biopsy.
- The clinical value of PSMA PET/MRI in the future.
- PSMA PET/MRI is unlikely to become a routine examination for the initial diagnosis of PCa in the short term, but it can serve as a supplement to mpMRI and has a certain diagnostic value.
- TP prostate biopsy is recommended.
- Targeted and systematic combined prostate biopsy will be the future development direction.
- Patients with lesions on mpMRI need targeted and systematic combined biopsy for the first biopsy.
- For patients with a prior negative biopsy but suspicious lesions on MRI, the choice between TB and SB for repeat biopsy should be based on the individual situation of the patient.
- FUS-TB is more standardized, and COG-TB is easier to expand. Both of them may be the future directions of TB.
- TB with a higher detection rate of csPCa and a lower detection rate of ciPCa than that of SB.
- Three cores may be recommended for TB; however, it should be decided individually.
- At least 10–12 cores are needed for TP SB.
- Free-hand TB cannot replace template TB within a short period, but it still can be performed in certain situations.

A delicate analysis will be more important in the future, and doctors will use advanced equipment to make decisions. With the advancement of technology in the future, the most essential aspect of performing a biopsy will be the doctors' strategy.

AUTHORS CONTRIBUTIONS

Study concept and design: Gang Song and Nianzeng Xing. *Acquisition of data*: All authors. *Analysis and interpretation of data*: Gang Song, Yajian Li, Yinbing Wang, Ruiyi Yan. *Drafting of the manuscript*: Gang Song, Yajian Li, Huimin Hou, Yichen Wang, Xuejuan Wang, Shaoxi Niu, Xiang Tu, Hongliang Shen, Zhien Zhou, Yinbing Wang, Ruiyi Yan, Ning Xu, and Gejun Zhang. *Critical revision of the manuscript for important intellectual content*: All authors. *Statistical analysis*: All authors. *Project administration*: Gang Song, Nianzeng Xing. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest except Nianzeng Xing (who is Editor-in-Chief of *UroPrecision*) and Gang Song (who is Deputy Editor-in-Chief of *UroPrecision*). They were excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article. Peer review was handled independently by the other editors to minimize bias.

ETHICS STATEMENT

Not applicable.

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