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Comprehensive Evaluation of Targeted and Perilesional Biopsy in Biopsy-Naïve Patients With Prostate Positive Magnetic Resonance Imaging: PERI-PRO Noninferiority Randomized Controlled Trial

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Study Need and Importance: The combined targeted and systematic biopsy (CTSBx) was the standard scheme for patients with visible suspicious lesions on MRI in recent years. 2024 European Association of Urology guideline recommended targeted and perilesional biopsy (TPLBx) for the diagnosis of patients with MRI visible suspicious lesions. This randomized controlled trial aims to comprehensively evaluate the efficacy and safety profiles of TPLBx and CTSBx schemes.

What We Found: This noninferiority randomized controlled trial provides high-level evidence to date comprehensively evaluating the diagnostic efficacy and safety profiles of TPLBx scheme and the routine CTSBx scheme (Figure). The results demonstrated that for patients with a single suspicious lesion on prostate multiparametric MRI, the Grade Group (GG) $\geq$ 2 cancer (GG $\geq$ 2-PCa; 58.4% vs 57.9%, risk difference [RD]: 0.5% [95% CI: −9.4% to 10.5%]), and GG $\geq$ 3-PCa (30.0% vs 29.5%, RD: 0.5% [95% CI: −8.7% to 9.7%]) detection rates of TPLBx were noninferior to that of CTSBx ($P < .001$). There was no significant difference in PCa and GG1-PCa detection rates between the 2 groups ($P > .05$). The complication rate of TPLBx was significantly lower than that of the CTSBx group (Clavien-Dindo scale $\geq$ 1: 62.1% vs 73.7%, $P = .023$), especially for bleeding-related complications (rectal bleeding: 34.0% vs 47.6%, $P = .003$; hematuria, 38.8% vs 55.6%, $P < .001$) and rectal pain (24.5% vs 34.4%, $P = .018$). Compared with CTSBx, TPLBx significantly shortened the procedure time and saved the pathological examination cost. TPLBx could be an alternative for the optimization of the biopsy scheme.

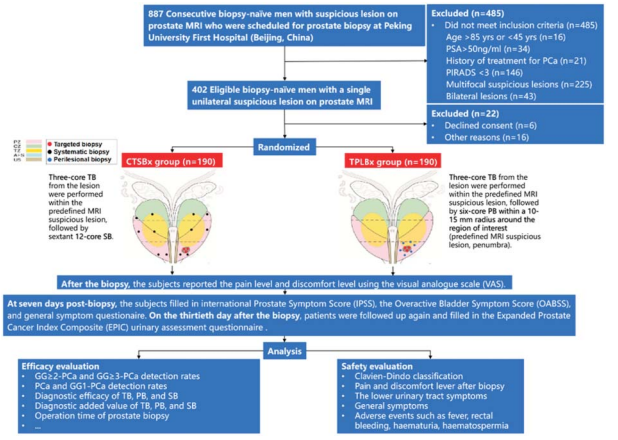

Figure. Study flowchart. A total of 380 eligible patients were randomized to the targeted and perilesional biopsy (TPLBx; n = 190) and combined targeted and systematic biopsy (CTSBx) groups (n = 190). EPIC-Urinary indicates the University of California, Los Angeles-Expanded Prostate Cancer Index Composite; GG, Grade Group; PB, perilesional biopsy; PCa, prostate cancer; PIRADS, Prostate Imaging Reporting and Data System; SB, systematic biopsy; TB, targeted biopsy.

Limitations: The single-center design limited the generalizability. Further efforts are required to validate these findings through large-scale, multicenter studies.

Interpretation for Patient Care: For patients with a single suspicious lesion on prostate multiparametric MRI, TPLBx could not only achieve the noninferior diagnostic efficiency of GG $\geq$ 2-PCa to the CTSBx with fewer biopsy cores but also significantly reduce the rate of some post-biopsy complications. TPLBx could shorten the procedure time and saved the pathological examination cost.

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Comprehensive Evaluation of Targeted and Perilesional Biopsy in Biopsy-Naïve Patients With Prostate Positive Magnetic Resonance Imaging: PERI-PRO Noninferiority Randomized Controlled Trial

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Purpose: The combined targeted and systematic biopsy (CTSBx) was the standard scheme for patients with visible suspicious lesions on MRI in recent years. 2024 European Association of Urology guideline recommended targeted and perilesional biopsy (TPLBx) for the diagnosis of patients with MRI-visible suspicious lesions. This randomized controlled trial aims to comprehensively evaluate the efficacy and safety profiles of TPLBx and CTSBx schemes.

Materials and Methods: A single-center noninferiority randomized controlled trial consecutively enrolled 380 biopsy-naïve patients (CTSBx: n = 190, TPLBx: n = 190) with a single unilateral suspicious lesion on prostate MRI from June 2024 to November 2024. The noninferiority margin was −15%. All biopsies were undertaken transrectally through the cognitive fusion technique. The primary outcome was Grade Group (GG) ≥ 2 cancer (GG ≥ 2-PCa) detection rate.

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Conflict of Interest Disclosures: The Authors have no conflicts of interest to disclose.

Ethics Statement: In lieu of a formal ethics committee, the principles of the Helsinki Declaration were followed. All human subjects provided written informed consent with guarantees of confidentiality.

Author Contributions:

Conception and design: Zhou, Gong, Liu, Wu, Deng.
Data acquisition: Li, Shang, Cai, Shen, Tian, Hu, Wu.
Data analysis and interpretation: Qiu, Shang, Deng, Wu.
Critical revision of the manuscript for scientific and factual content: Li, Shang, Qiu, Zhou, Wu, Gong, Cai, Shang, Shen, Tian, Hu, Liu.
Drafting the manuscript: Deng.
Statistical analysis: Shang, Qiu, Zhou, Shang, Deng, Wu.
Supervision: Li, Gong, Cai, Shen, Tian, Hu, Liu, Wu.

Data Availability: The data and materials generated in this study are available from the corresponding author on reasonable request.

Data Access and Responsibility: Kan Gong and Yi Liu have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Results: The GG $\geq$ 2-PCa (58% vs 58%, risk difference [RD]: 0.53% [95% CI: −9.4% to 11%]) and GG $\geq$ 3-PCa (30% vs 30%, RD: 0.53% [95% CI: −8.7% to 9.7%]) detection rates of TPLBx were noninferior to that of CTSBx ($P < .001$). There was no significant difference in PCa and GG1-PCa detection rates between the 2 groups ($P > .050$). The complication rate of TPLBx was significantly lower than that of CTSBx group (Clavien-Dindo scale $\geq$ 1: 62% vs 74%, $P = .023$), especially for bleeding-related complications (rectal bleeding: 34% vs 48%, $P = .003$; hematuria, 39% vs 56%, $P < .001$) and rectal pain (25% vs 34%, $P = .018$). TPLBx could significantly shorten the procedure time and saved the pathological cost ($P < .001$).

Conclusions: For patients with a single unilateral suspicious lesion on prostate MRI, TPLBx achieved the noninferior diagnostic efficacy of clinically significant PCa and better safety than the CTSBx scheme.

Trial Registration: ClinicalTrials.gov Identifier: NCT06482658

Key Words: grade group $\geq$ 2 prostate cancer, perilesional biopsy, targeted biopsy, systematic biopsy

PROSTATE biopsies have been the cornerstone of prostate cancer (PCa) diagnosis, risk stratification, and treatment planning.[1] Combined targeted and systematic biopsy (CTSBx) could effectively detect Grade Group (GG) $\geq$ 2 PCa (GG $\geq$ 2-PCa) and was the standard scheme for biopsy-naive patients who have a suspicious lesion on MRI.[2] However, the increased number of biopsy-cores would lead to overdiagnosis and elevate the risk of complications.[3-6] Hence, there is an urgent need to optimize biopsy schemes by maximizing the GG $\geq$ 2-PCa detection while reducing overdiagnosis and improving safety.

The optimal biopsy scheme should maximize the GG $\geq$ 2-PCa detection with the most accurate core sites and the least biopsy cores.[4] Recent studies demonstrated that most of the GG $\geq$ 2-PCa were found within a band of 10-mm radius outside MRI lesions (the penumbra).[7] Therefore, focusing biopsy cores within and around the region of interest (ROI), known as targeted and perilesional biopsy (TPLBx), is recommended by the latest European Association of Urology (EAU) guideline for patients with visible suspicious lesions on MRI.[1] Many studies have preliminarily verified that the diagnostic efficacy of TPLBx was not inferior to that of CTSBx with the benefits of reducing biopsy cores.[3,5,6,8-10] However, data are mostly retrospective. The safety profile warrants further evaluation. There is still a lack of high-quality, prospective evidence for the TPLBx scheme. Thus, this randomized controlled trial (RCT) aims to evaluate the efficacy and safety of TPLBx and CTSBx and provide high-quality evidence for optimizing prostate biopsy schemes.

MATERIALS AND METHODS

Trial Design

This is a single-center noninferiority RCT for biopsy-naive patients with a suspicious lesion on prostate MRI (NCT06482658). The study was reviewed and approved by the Institutional Review Board of Peking University First Hospital (2024-341). Written informed consents were obtained from subjects.

Subjects and Outcomes

From June 2024 to November 2024, consecutive biopsy-naive men with positive MRI who were scheduled for prostate biopsy were evaluated for eligibility. The inclusion criteria were (1) age between 45 and 85 years; (2) no previous biopsy; (3) high MRI quality (Prostate Imaging Quality score $\geq$ 3)[11]; (4) presence of a single unilateral suspicious lesion; (5) in accordance with the EAU guideline for performing perilesional biopsy (PB; Prostate Imaging Reporting and Data System [PI-RADS $\geq$ 4 or PI-RADS = 3], clinical suspicion of PCa)[1]; (6) PSA $\leq$ 50 ng/mL. The exclusion criteria were (1) contraindication for MRI examination or biopsy; (2) a history of radiotherapy, chemotherapy, androgen deprivation therapy, or surgery; (3) previous biopsy; (4) multifocal suspicious lesions. The detailed inclusion and exclusion criteria were shown in Supplementary materials (https://www.jurology.com).

The primary outcome was the GG $\geq$ 2-PCa detection rate. The secondary outcomes included the PCa and GG1-PCa detection rates, complication rate, biopsy time, and the costs for pathological processing.

Randomization and Masking

Eligible subjects were randomized at a ratio of 1:1 to TPLBx or CTSBx group. Randomization was achieved by using a computer-generated list of random numbers, which was password-protected in a central database to ensure the allocation concealment. Subjects were allocated by independent research nurses. The allocation information was informed to the operator before biopsy, while being undisclosed from the patients and pathologists who assessed the histology.

Procedure

MRI examinations were performed using the 3-T scanners. The images were evaluated according to PI-RADS V2.1 by 2 genitourinary radiologists with > 10 years of experience in prostate MRI. Before the biopsy, patients filled in questionnaires regarding the lower urinary tract symptoms using the International Prostate Symptom Score, regarding the urination function using the Overactive Bladder Symptom Score (OABSS), and the Expanded PCa Index Composite (EPIC) Urinary assessment questionnaire.[12] All questionnaires were validated

in Chinese. Prophylactic antibiotics (usually cephalosporins) was routinely used from 1 day before the biopsy to 1 day after the biopsy. Bowel preparation was conducted 1 day before and on the day of the biopsy. Povidone iodine was routinely used to clean rectum before the biopsy. All biopsies were undertaken transrectally through the cognitive fusion technique. Two highly experienced urologists independently conducted targeted biopsy (TB)/PB and systematic biopsy (SB). The graphical illustration of CTSBx and TPLBx is shown in Figure 1. For TPLBx group, 3-core TB was obtained within the predefined MRI suspicious lesion (ROI), followed by ring-distributed 6-core PBs within a 10 to 15 mm radius around the ROI. The location of PB cores depended on the shape and location of the ROI. Regarding CTSBx, 3-core TBs were firstly performed, followed by sextant 12-core SBs independently conducted by another urologist. The procedure time was calculated from the probe inserting into the rectum to the end of the biopsy. After the biopsy, patients were followed up and filled in the above questionnaires under the instruction of research nurses on the 7th day. On the 30th day, patients filled in the EPIC-Urinary questionnaires. The occurrence of complications/adverse events were graded using the Clavien-Dindo classification.[13]

Each biopsy core was placed in an individual container and was firstly assessed by a uropathologist (Q.S.) who was blinded to the allocation. Then another uropathologist (S.H.) independently reported the global GG based on the total extent of all biopsy cores according to the recommendations of the International Society of Urological Pathology (ISUP).[1,14]

Sample Size

According to previous publications and preliminary experiment results,[15,16] it was hypothesized that the GG $\geq$ 2-PCa detection rates of TPLBx and CTSBx were both 55%. A parallel, 2-group design were used to test whether the GG $\geq$ 2-PCa detection rate of TPLBx (P_1) is noninferior to that of CTSBx (P_2), with a noninferiority margin of -0.15 (H_0: P_1-$P_2 \leq -0.15$, H_1: P_1-$P_2 > -0.15$). The comparison was made using a 1-sided, 2-sample Z-test (unpooled) with type-I error rate (α) of .025. The reference group proportion was assumed to be 0.55. To detect a proportion difference (P_1-P_2) of 0 with 80% power, the number of subjects needed would be 173 in TPLBx group (treatment) and 173 in CTSBx group (reference). To account for potential dropout and the effect of stratification, the sample size was inflated by 10%, resulting in a total of 380 subjects.

Statistical Analysis

All statistical analyses were performed with R 4.3.1. Clinical characteristics were summarized as mean $\pm$ SD for normally distributed data or median (IQR) for skewed data and frequencies for categorical variables. The Newcombe-Wilson method was used to calculate the 2-sided 95% CI for the difference in GG $\geq$ 2-PCa detection rate (primary outcome) and to test the noninferiority hypothesis between TPLBx and CTSBx groups. Noninferiority was established if the lower bound of the CI exceeded -15% and the one-sided noninferiority hypothesis was statistically significant at the prespecified alpha level of .025 ($P < .025$). Some urologists defined the clinically significant PCa (csPCa) as GG $\geq$ 2-PCa. However, some other urologists suggested to alter the definition of csPCa to GG $\geq$ 3-PCa. Considering the inconsistent definition, the GG $\geq$ 3-PCa detection rate was prespecified analyzed to act as a sensitivity analysis of the primary outcome. Secondary outcomes, including PCa and GG1-PCa detection rates, complication rates (categorical variables, analyzed with χ^2/Fisher exact tests), biopsy time, and pathological costs (quantitative variables, analyzed using independent t tests for normally distributed data or Mann-Whitney U-tests for non-normal distributions, with normality determined by assessment of histograms and Q-Q plots) were analyzed with 2-sided $\alpha = .05$. Maximum cancer core involvements and proportion of positive cores were compared to explore. Given the multiple

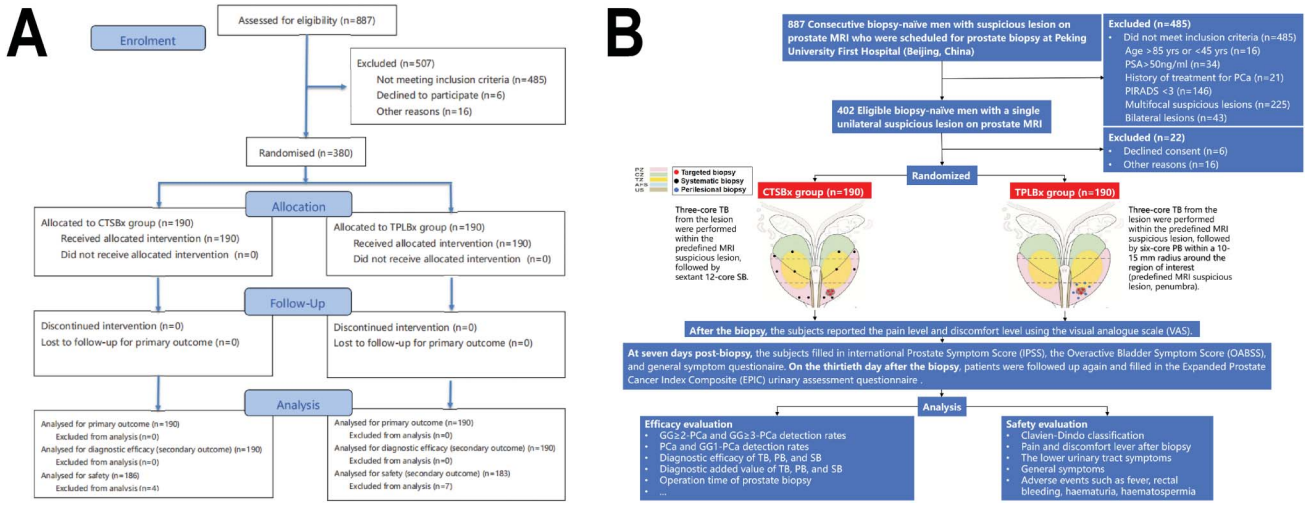

Figure 1. A, CONSORT (Consolidated Standards of Reporting Trials) flow diagram. B, Study flowchart. CTSBx indicates combined targeted and systematic biopsy; EPIC-Urinary, the University of California, Los Angeles-Expanded Prostate Cancer Index Composite; GG, Grade Group; PB, perilesional biopsy; PCa, prostate cancer; PIRADS, Prostate Imaging Reporting and Data System; SB, systematic biopsy; TB, targeted biopsy; TPLBx, targeted and perilesional biopsy.

comparisons (SB, ipsilateral-SB, contralateral-SB, or PB vs TB), we applied Bonferroni correction to maintain an experiment-wise error rate of $\alpha = .05$. Prespecified subgroup analyses applied the same group-comparison approaches, no more statistical adjustments (eg, between different subgroups) were implemented to account for multiple comparisons in the current analyses. Other than the primary analysis, a 2-sided alpha level of .05 was applied for all exploratory analyses of secondary end points. No missing data imputation was performed in this study, and all analyses were conducted using complete cases only.

RESULTS

Subjects Characteristics

A total of 380 eligible patients were randomized to the TPLBx (n = 190) and CTSBx groups (n = 190; Figure 1). The prebiopsy characteristics were comparable (Table 1).

Primary Outcome

The GG $\geq$ 2-PCa detection rate of TPLBx group was 58% (95% CI: 51%-65%), which was noninferior to that of CTSBx group (58% [95% CI: 51%-65%]; Table 2). The noninferiority hypothesis was tested using the Newcombe-Wilson method with a prespecified margin of $\Delta = -15\%$. The risk difference (RD) between the 2 groups was 0.53% (95% CI: −9.4% to 11%), the lower bound (−9.4%) exceeded the noninferiority margin (−15%), supporting the conclusion of noninferiority ($P = .001$). As a sensitivity analysis of the primary outcome, there was no statistically significant difference in GG $\geq$ 3-PCa detection rate between the 2 groups (TPLBx: 30%, CTSBx: 30%, RD: 0.53% [95% CI: −8.7% to 9.7%]), supporting the conclusion of noninferiority ($P < .001$).

Secondary Outcomes

Diagnostic Performance. There was no statistically significant difference in PCa (TPLBx: 64%, CTSBx: 69%, $P = .4$) and GG1-PCa (TPLBx: 5.8%, CTSBx: 11%, $P = .096$) detection rates between the 2 groups. No significant difference was observed in ISUP distribution (Table 2, $P = .5$). The proportion of positive cores in the TPLBx group was significantly higher than that in the CTSBx group ($P = .001$).

To further explore the role of TB, SB, and PB in diagnoses, we calculated their diagnostic efficiency and added value according to different types of biopsy and distribution of SB (Figures 2 and 3; Table 3). The GG $\geq$ 2-PCa, GG $\geq$ 3-PCa, and PCa detection rates of PB were 54%, 25%, and 61%, with the added value of 4.2%, 1.1%, and 4.2%, respectively. The added value of SB was 4.7%, 1.6%, and 5.8% for the detection of GG $\geq$ 2-PCa, GG $\geq$ 3-PCa, and PCa, respectively. The GG $\geq$ 2-PCa detection rates of ipsilateral-SB and contralateral-SB were 48% and 13%. The ipsilateral-SB contributed to the

Table 1. *Baseline Characteristics Before Biopsy*

Characteristics	CTSBx group (n = 190)	TPLBx group (n = 190)	*P* value
Age, median (IQR)	67 (61-71)	68 (61-72)	.7
BMI, median (IQR)	24.2 (22.7-26.4)	24.5 (23.1-26.7)	.20
No. DRE (%)			
Negative	23 (12)	12 (6.3)	.10
Suspicious	114 (60)	129 (68)	
Positive	53 (28)	49 (26)	
PSA, median (IQR)	9.0 (6.3-13.2)	8.2 (5.8-12.1)	.13
Prostate volume, median (IQR)	37.8 (29.5-58.5)	41.4 (31.2-57.0)	.3
PSA density, median (IQR)	0.21 (0.15-0.35)	0.21 (0.12-0.30)	.077
No. PIRADS (%)			
3	48 (25)	50 (26)	.9
4	93 (49)	89 (47)	
5	49 (26)	51 (27)	
No. laterality (%)			
Left	102 (54)	87 (46)	.15
Right	88 (46)	103 (54)	
No. zone (%)			
PZ	119 (63)	127 (67)	.7
TZ	68 (36)	60 (32)	
PZ + TZ	3 (1.6)	3 (1.6)	
Maximum lesion diameter, median (IQR)	1.2 (0.9-1.6)	1.2 (0.9-1.6)	1
No. ultrasound result (%)			
Invisible/benign lesion	65 (34)	73 (38)	.5
Malignant lesion	125 (66)	117 (62)	
OABSS total score before biopsy, median (IQR)	4 (2-6)	3 (2-5)	.081
IPSS total score before biopsy, median (IQR)	9 (5-16)	10 (4-17)	.3
EPIC-urinary total score before biopsy, median (IQR)	19 (17-19)	19 (17-19)	.5
EPIC-urinary quality of life before biopsy, median (IQR)	1 (0-2)	1 (0-2)	1

Abbreviations: CTSBx, combined targeted and systematic biopsy; DRE, digital rectal examination; EPIC-Urinary, Expanded Prostate Cancer Index Composite-Urinary domain; IPSS, International Prostate Symptom Score; OABSS, overactive bladder symptom score; PIRADS, Prostate Imaging Reporting and Data System; PZ, peripheral zone; TPLBx, targeted and perilesional biopsy; TZ, transition zone.

Table 2. *Clinicopathological Characteristics After Biopsy*

Characteristics	CTSBx group (n = 190)		TPLBx group (n = 190)		*P* value
Primary end point					
GG ≥2-PCa					
Detection rate (95% CI)	58%	(51%-65%)	58%	(51%-65%)	1
RD (95% CI)	0.53%	(−9.4% to 11%)			**< .001**[a]
GG ≥3-PCa					
Detection rate (95% CI)	29%	(23%-36%)	30%	(23%-37%)	1
RD (95% CI)	0.53%	(−8.7% to 9.7%)			**< .001**[a]
Secondary end points					
PCa					
Detection rate (95% CI)	69%	(62%-76%)	64%	(57%-71%)	.4
RD (95% CI)	−4.7%	(−14% to 4.8%)			
GG1-PCa					
Detection rate (95% CI)	11%	(6.6%-16%)	5.8%	(2.5%-9.1%)	.096
RD (95% CI)	−5.3%	(−11% to 0.27%)			
ISUP of biopsy specimens (%)					
No PCa	59	(31)	68	(36)	.5
GG1	21	(11)	11	(5.8)	
GG2	54	(28)	54	(28)	
GG3	38	(20)	42	(22)	
GG4	7	(3.7)	5	(2.6)	
GG5	11	(5.8)	10	(5.3)	
No. of biopsy cores, median (IQR)	15	(15-15)	9	(9-9)	**< .001**
Proportion of positive cores, median (IQR), %	27	(0-58)	44	(0-89)	**.001**
Maximum cancer core involvements, median (IQR), %	50	(0-90)	65	(0-90)	1
Total procedural time, median (IQR), s	235	(220-259)	168	(150-188)	**< .001**
Cost of pathological examination, median (IQR), $	75.9	(75.9-75.9)	50.6	(50.6-50.6)	**< .001**
OABSS total score after biopsy, median (IQR)	3	(2-6)	3	(2-4)	**.013**
IPSS total score after the biopsy, median (IQR)	7	(3-14)	8	(3-13)	.8
EPIC-urinary total score after biopsy, median (IQR)	18	(15-19)	19	(15-19)	.2
EPIC-urinary quality of life after the biopsy, median (IQR)	1	(0-2)	1	(0-2)	.5
Clavien-Dindo grade (%)					
No adverse event	50	(26)	72	(38)	**.023**
Grade 1	138	(73)	118	(62)	
Grade 2	2	(1.1)	0	(0)	
Grade 3, 4, 5	0	(0)	0	(0)	
Pain level (VAS), mean (SD)	3.0	(1.5)	2.9	(1.6)	.7
Discomfort level, mean (SD)	3.5	(1.8)	3.4	(1.9)	.5

Abbreviations: CTSBx, combined targeted and systematic biopsy; EPIC-Urinary, the University of California, Los Angeles-Expanded Prostate Cancer Index Composite; GG, Grade Group; IPSS, International Prostate Symptom Score; ISUP, International Society of Urological Pathology; OABSS, overactive bladder symptom score; PCa, prostate cancer; RD, risk difference; TPLBx, targeted and perilesional biopsy; VAS, visual analog scale.
Bolded text indicates statistically significant result ($P < .05$).
[a] Non-inferior test.

main added value of SB (4.7%) for GG ≥ 2-PCa detection, while contralateral-SB contributed no added value (0) and increased the GG1-PCa detection.

Postbiopsy Complications. The response rate of postbiopsy questionnaires was 98%. The Clavien-Dindo scale ≥ 1 complication rate of TPLBx (62%) was significantly lower than that of CTSBx group (74%; $P = .023$). No grade 3/4/5 adverse events occurred (Table 2).

The prebiopsy urinary function was similar between the 2 groups (Table 1). The overall OABSS of TPLBx group was significantly lower than that of CTSBx group (Supplementary Table S1, https://www.jurology.com, $P = .013$). No statistically significant difference was observed in the overall International Prostate Symptom Score (Supplementary Table S2, https://www.jurology.com, $P = .8$) or EPIC-Urinary score (Supplementary Tables S3 and S4, https://www.jurology.com, $P = .2$) between the 2 groups.

Supplementary Table S5 (https://www.jurology.com) shows the general symptoms questionnaire. The local/systematic infection rate was very low (1.6%). Only one subject (0.53%) in the TPLBx group reported fever, while 5 subjects (2.7%) in the CTSBx group reported fever ($P = .10$). Subjects in the CTSBx group experienced more rectal pain (34% vs 25%, $P = .018$) than in the TPLBx group. The rates of rectal bleeding (48% vs 34%, $P = .003$) and hematuria (56% vs 39%, $P < .001$) were significantly higher in the CTSBx group than in the TPLBx group. The prevalence of other general symptoms was similar between the 2 groups ($P > .05$). Most subjects reported the occurrence of these symptoms as being no problem or a minor problem in routine life (Supplementary Table S5, https://www.jurology.com).

Procedure Time and Cost Analysis. Compared with CTSBx, TPLBx significantly shortened the procedure time (168 seconds [150 seconds-188 seconds] vs 235 seconds [220 seconds-259 seconds], $P < .001$),

No. of Patients (%) in ISUP GG with PB specimens

	TPLBx group	No PCa	GG1	GG2	GG3	GG4	GG5	Total
	No PCa	68 (36)	3 (1.6)	3 (1.6)	1 (0.53)	1 (0.53)	0 (0)	**76 (40)**
No. of	GG1	3 (1.6)	5 (2.6)	3 (1.6)	0 (0)	0 (0)	0 (0)	**11 (5.8)**
Patients (%)	GG2	1 (0.53)	3 (1.6)	44 (23)	0 (0)	0 (0)	0 (0)	**48 (25)**
in ISUP GG	GG3	2 (1.1)	2 (1.1)	5 (2.6)	29 (15)	0 (0)	0 (0)	**38 (20)**
with TB	GG4	0 (0)	0 (0)	0 (0)	3 (1.6)	4 (2.1)	0 (0)	**7 (3.7)**
specimens	GG5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10 (5.3)	**10 (5.3)**
	Total	**74 (39)**	**13 (6.9)**	**55 (29)**	**33 (17)**	**5 (2.6)**	**10 (5.3)**	**190 (100)**

Concordance
Upgrading by the PB
Downgrading by the PB

No. of Patients (%) in ISUP GG with SB specimens

	CTSBx group	No PCa	GG1	GG2	GG3	GG4	GG5	Total
	No PCa	59 (31)	8 (4.2)	2 (1.1)	0 (0)	0 (0)	1 (0.53)	**70 (37)**
No.of	GG1	5 (2.6)	8 (4.2)	6 (3.2)	0 (0)	0 (0)	0 (0)	**19 (10)**
Patients (%)	GG2	6 (3.2)	8 (4.2)	32 (17)	4 (2.1)	0 (0)	0 (0)	**50 (26)**
in ISUP GG	GG3	4 (2.1)	0 (0)	6 (3.2)	19 (10)	1 (0.53)	2 (1.1)	**32 (17)**
with TB	GG4	0 (0)	0 (0)	0 (0)	3 (1.6)	8 (4.2)	0 (0)	**11 (5.8)**
scheme	GG5	0 (0)	0 (0)	0 (0)	1 (0.53)	0 (0)	7 (3.7)	**8 (4.2)**
	Total	**74 (39)**	**24 (13)**	**46 (24)**	**27 (14)**	**9 (4.7)**	**10 (5.3)**	**190 (100)**

Concordance
Upgrading by the SB
Downgrading by the SB

Figure 2. Cross-tabulation of the highest International Society of Urological Pathology (ISUP) Grade Group (GG) of different biopsy specimens. CTSBx indicates combined targeted and systematic biopsy; PB, perilesional biopsy; PCa, prostate cancer; SB, systematic biopsy; TB, targeted biopsy; TPLBx, targeted and perilesional biopsy.

decreased the number of consumables, and saved the pathological examination cost (Table 2, $50.6 vs $75.9).

Subgroup Analysis

In the prespecified subgroups stratified according to age, PSA, PI-RADS, and lesion size (cut-off: 10 mm),

No. of Patients (%) in ISUP GG with ipsilateral-SB specimens

	CTSBx group	No PCa	GG1	GG2	GG3	GG4	GG5	Total
	No PCa	63 (33)	4 (2.1)	2 (1.1)	0 (0)	0 (0)	1 (0.53)	**70 (37)**
No.of	GG1	5 (2.6)	8 (4.2)	6 (3.2)	0 (0)	0 (0)	0 (0)	**19 (10)**
Patients (%)	GG2	7 (3.7)	7 (3.7)	32 (17)	4 (2.1)	0 (0)	0 (0)	**50 (26)**
in ISUP GG	GG3	4 (2.1)	0 (0)	6 (3.2)	19 (10)	1 (0.53)	2 (1.1)	**32 (17)**
with TB	GG4	0 (0)	0 (0)	0 (0)	3 (1.6)	8 (4.2)	0 (0)	**11 (5.8)**
scheme	GG5	0 (0)	0 (0)	0 (0)	1 (0.53)	0 (0)	7 (3.7)	**8 (4.2)**
	Total	**79 (42)**	**19 (10)**	**46 (24)**	**27 (14)**	**9 (4.7)**	**10 (5.3)**	**190 (100)**

Concordance

Upgrading by the ipsilateral-SB

Downgrading by the ipsilateral-SB

No. of Patients (%) in ISUP GG with contralateral-SB specimens

	CTSBx group	No PCa	GG1	GG2	GG3	GG4	GG5	Total
	No PCa	64 (34)	6 (3.2)	0 (0)	0 (0)	0 (0)	0 (0)	**70 (37)**
No.of	GG1	11 (5.8)	8 (4.2)	0 (0)	0 (0)	0 (0)	0 (0)	**19 (10)**
Patients (%)	GG2	32 (17)	4 (2.1)	14 (7.4)	0 (0)	0 (0)	0 (0)	**50 (26)**
in ISUP GG	GG3	23 (12)	4 (2.1)	3 (1.6)	2 (1.1)	0 (0)	0 (0)	**32 (17)**
with TB	GG4	8 (4.2)	0 (0)	0 (0)	2 (1.1)	1 (0.53)	0 (0)	**11 (5.8)**
scheme	GG5	6 (3.2)	0 (0)	2 (1.1)	0 (0)	0 (0)	0 (0)	**8 (4.2)**
	Total	**144 (76)**	**22 (12)**	**19 (10)**	**4 (2.1)**	**1 (0.53)**	**0 (0)**	**190 (100)**

Concordance

Upgrading by the contralateral-SB

Downgrading by the contralateral-SB

Figure 2. Continued.

the diagnosis performance of TPLBx was non-inferior to that of CTSBx (Supplementary Table S6, https://www.jurology.com, Figure 4). However, in patients aged 45 to 65 years and patients with $\geq$ 10 mm lesions, CTSBx detected significantly more GG1-PCa ($P < .05$). The ISUP distribution of

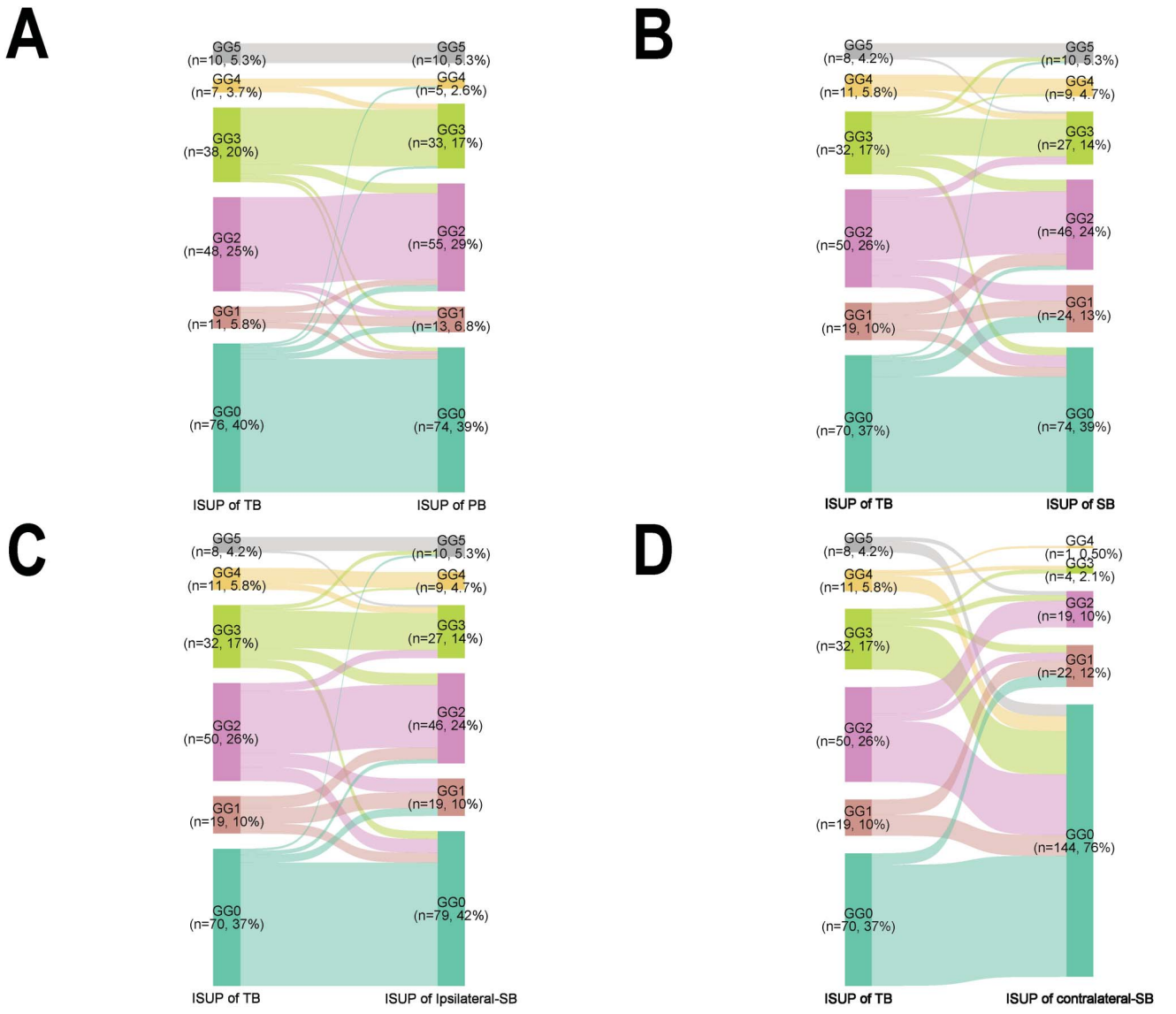

Figure 3. A, International Society of Urological Pathology (ISUP) Grade Group (GG) of targeted biopsy (TB) and perilesional biopsy (PB) specimens among patients of targeted and perilesional biopsy group. B, ISUP GG of TB and systematic biopsy (SB) specimens among patients of combined targeted and systematic biopsy group. C, ISUP GG of TB and ipsilateral-SB specimens among patients of combined targeted and systematic biopsy group. D, ISUP GG of TB and contralateral-SB specimens among patients of combined targeted and systematic biopsy group.

patients with different PI-RADS was shown in Table 4.

DISCUSSION

Although CTSBx could effectively detect GG $\geq$ 2-PCa and was the standard scheme in recent years, it is essential to balance the goals of maximal GG $\geq$ 2-PCa detection, minimal GG1-PCa detection, safety, and cost-effectiveness.[17] The latest EAU guideline recommended TPLBx for patients with visible suspicious lesions on MRI.[1] In this RCT, we demonstrated that for biopsy-naive patients with a single unilateral suspicious lesion on MRI, the cancer detection rate of TPLBx was noninferior to that of CTSBx.

Current PCa diagnostic pathway using imaging as the main indication for biopsy. ROI in MRI is highly predictive of GG $\geq$ 2-PCa and biopsy cores are more efficient due to targeting,[18] which was also confirmed by our analysis (Figure 2 and Table 3). Missing GG $\geq$ 2-PCa on TB is associated with imprecise lesion registration, lesion volume underestimation, and cognitive fusion targeting errors.[19] While segmentation inaccuracies are less critical in large lesions, small lesion mistargeting may reduce GG $\geq$ 2-PCa detection.[20] The importance of PB may be greater in cases of segmentation mismatch and at risk for targeting errors.[20] The distance range from the edge of ROI is debated. Brisbane et al demonstrated that 90% of GG $\geq$ 2-PCa detected by SB

Table 3. *Diagnosis Efficacy and Added Value of Targeted Biopsy, Systematic Biopsy, Ipsilateral-Systematic Biopsy, Contralateral-Systematic Biopsy, and Perilesional Biopsy Regarding to the Lesion Location*

Biopsy scheme	GG ≥2-PCa detection rate (%)	GG ≥2-PCa added value (%)	GG ≥3-PCa detection rate (%)	GG ≥3-PCa added value (%)	PCa detection rate (%)	PCa added value (%)	Maximum cancer core involvements (%), median (IQR)	*P* value[a]	Proportion of positive cores, median (IQR)	*P* value[a]
CTSBx (n = 190)	110 (58)		54 (28)		131 (69)					
TB[b]	101 (53)	18 (9.5)	51 (27)	9 (4.7)	120 (63)	15 (7.9)	40 (0-90)	Reference	67 (0-100)	Reference
SB[c]	92 (48)	9 (4.7)	46 (24)	3 (1.6)	116 (61)	11 (5.8)	20 (0-70)	**.001**	8.3 (0-33)	**< .001**
Ipsilateral-SB[d]	92 (48)	9 (4.7)	46 (24)	3 (1.6)	111 (58)	7 (3.7)	20 (0-70)	**< .001**	17 (0-50)	**< .001**
Contralateral-SB[e]	24 (13)	0 (0)	5 (2.6)	0 (0)	46 (24)	6 (3.2)	0 (0-0)	**< .001**	0 (0-0)	**< .001**
TPLBx (n = 190)	111 (58)		57 (30)		122 (64)					
TB[f]	103 (54)	8 (4.2)	55 (29)	9 (4.7)	114 (60)	6 (3.2)	50 (0-80)	Reference	67 (0-100)	Reference
PB[g]	103 (54)	8 (4.2)	48 (25)	2 (1.1)	116 (61)	8 (4.2)	40 (0-80)	.3	33 (0-83)	**< .001**

Abbreviations: CTSBx, combined targeted and systematic biopsy; GG, Grade Group; PB, perilesional biopsy; PCa, prostate cancer; SB, systematic biopsy; TB, targeted biopsy; TPLBx, targeted and perilesional biopsy.
Bolded text indicates statistically signnificant result ($P < .05$).
[a] Bonferroni correction was used to maintain an experiment-wise error rate of $\alpha = .05$.
[b] The added value of TB in the CTSBx group was defined as any GG ≥2-PCa, GG ≥3-PCa, or PCa detection through TB among patients with negative SB.
[c] The added value of SB in the CTSBx group was defined as any GG ≥2-PCa, GG ≥3-PCa, or PCa detection through SB among patients with negative TB.
[d] The added value of ipsilateral-SB in the CTSBx group was defined as any GG ≥2-PCa, GG ≥3-PCa, or PCa detection through ipsilateral-SB among patients with negative TB.
[e] The added value of contralateral-SB in the CTSBx group was defined as any GG ≥2-PCa, GG ≥3-PCa, or PCa detection through contralateral-SB among patients with negative TB.
[f] The added value of TB in the TPLBx group was defined as any GG ≥2-PCa, GG ≥3-PCa, or PCa detection through PB among patients with negative PB.
[g] The added value of PB in the TPLBx group was defined as any GG ≥2-PCa, GG ≥3-PCa, or PCa detection through TB among patients with negative TB.

were found from a range of 10 mm from the ROI edges.[7] Raman et al[3] reported that 94% of SB cores containing GG ≥ 2-PCa were found within 15 mm from the ROI edge. Comprehensively considering the possible locating error during the cognitive fusion biopsy and the results from previous publications, we determined that the distance from ROI to 10-15 mm was the range of PB. In addition, Martin et al[21] proposed the best strategy would be targeting the ROI center with additional peripherally ring-distributed PB cores to mitigate targeting errors in their large-scale cohort study. Furthermore, the optimal number of PB cores is unclear. There is significant heterogeneity regarding the number of PB cores.[6] The previous meta-analysis reported the median (IQR) number of cores for TPLBx was 9.5 (7.5-12.3).[10] Therefore, we chose 9-core TPLBx consisting of 3-core TB and 6-core ring-distributed PB around the ROI, which led to 103/111 (93%) GG ≥ 2-PCa detection, validating the effectiveness of this strategy. In this RCT, 3-core TB identified 204/221 (92%) GG ≥ 2-PCa, led to relatively low added value of SB (4.7%), ipsilateral SB (4.7%), and PB (4.2%) compared with previous studies.[22,23] The contralateral SB contributed no added value for GG ≥ 2-PCa detection but increased the GG1-PCa detection, indicating that it could be omitted. The maximum cancer core involvement of TB cores was significantly higher than that of SB cores ($P < .001$) but was similar to that of PB cores ($P = .3$), further proving the ability of PB for detecting GG ≥ 2-PCa.

TPLBx provides diagnostic precision for ROI, which may enable focal therapy (FT) implementation. As a novel treatment, FT offers an intermediate strategy for localized PCa, balancing the conservative approach of active surveillance against the morbidity risks of whole-gland treatments.[24] Previous studies reported that since multiparametric MRI underestimates tumor size, a safety margin of ≥ 10 mm is recommended for personalized FT to achieve complete treatment.[25] TPLBx, whose biopsy cores focusing in and around the ROI, could achieve accurate identification and enhance treatment precision by defining tumor regions and boundaries.[26] Therefore, it may be an appropriate scheme for guiding FT. However, FT is still considered investigational in international PCa guidelines.[1,2] A critical barrier to conducting FT is the absence of standardized patient selection criteria. Most current preoperative risk assessment tools rely on the biopsy of the whole prostate. As TPLBx scheme gains traction, the updated risk stratification and assessment tools are warranted to develop.

Another important profile is safety. The role of biopsy has changed from pure detection to overall management of patients.[27] There is a dearth of research available evaluating complications, postbiopsy urinary function, and patient perception. The complication rate of TPLBx was significantly lower than that of CTSBx ($P = .023$). The infectious rate was very low. Performing TPLBx and reducing biopsy cores were related to significantly decreased risk of bleeding complications. Although the OABSS of TPLBx was significantly lower than that of CTSBx, it should be noted that according to the previous publications, the minimal clinically important change of the OABSS is −3. Therefore, the difference of OABSS was statistically significant but not clinically significant.[28] TPLBx could significantly reduce the postbiopsy rectal pain, improving

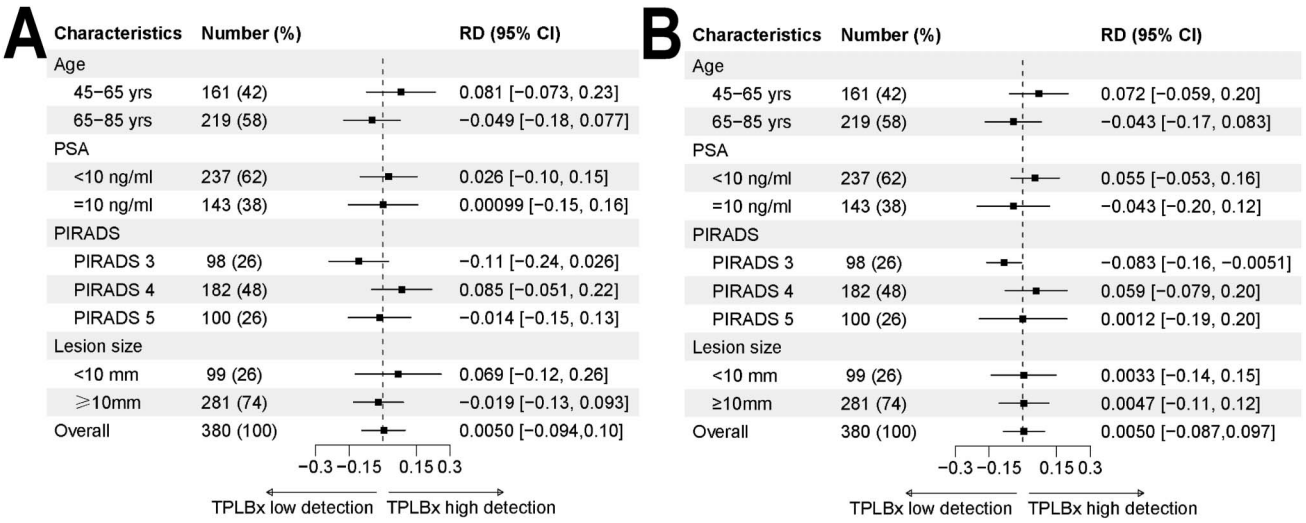

Figure 4. Forest plot of subgroup analysis for (A) GG ≥ 2-PCa and (B) GG ≥ 3-PCa detection rates in the TPLBx and CTSBx group. CTSBx indicates combined targeted and systematic biopsy; GG, Grade Group; PCa, prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System; RD, rate difference; TPLBx, targeted and perilesional biopsy.

the quality of life. The overall rate and severity of most complications are within acceptable limits and self-limiting, providing the safety support for the TPLBx scheme.

From the perspective of health economics, appropriately reducing the number of cores while maintaining the GG ≥ 2-PCa detection is worthy of encouragement. Compared with CTSBx, TPLBx significantly shortened the procedure time, improved the efficiency, decreased the number of consumables, and saved the pathological examination cost. Shorter procedure duration could not only decrease the burden of technical time and workload on pathology departments, leading to the release of more resources, but also reduce the pain accumulation during the biopsy.[29] Preventing overdiagnosis of GG1-PCa and avoiding the impaired quality of life because of complications would substantially save the subsequent medical costs and optimize medical resource utilization.[30]

This study is important for several reasons. First, this high-quality RCT provide strong evidence supporting TPLBx as a valuable strategy for GG ≥ 2-PCa detection in patients with a single unilateral suspicious lesion on prostate MRI, address the gap in the safety and health economics profile. Second, the prospective enrollment was consecutive and the randomization was strictly performed, guaranteeing the high quality in data collection. However, there are still some limitations. First, the single-center design would limit the generalization of the results. Nevertheless, as one of the largest urology centers in China, more than 1600 prostate biopsies are performed annually. Approximately half of these patients were referred from diverse regions nationwide, contributing to a substantial level of population representativeness. We are conducting the large-scale, multicenter RCT to further validate the results (NCT06482645). Second, owing to the relatively short period, the number of patients receiving surgery was limited. We are continuing to follow up the patient and collect the radical prostatectomy specimens to further explore the lesion characteristics on both MRI and whole-mount slices. The long-term clinical outcomes and

Table 4. *International Society of Urological Pathology Grade Group of Patients With Different Prostate Imaging Reporting and Data System Scores in CTSBx Group and TPLBx Group*

	PIRADS 3 (%)			PIRADS 4 (%)			PIRADS 5 (%)		
GG	CTSBx (n = 48)	TPLBx (n = 50)	*P* value	CTSBx (n = 93)	TPLBx (n = 89)	*P* value	CTSBx (n = 49)	TPLBx (n = 51)	*P* value
No PCa	33 (69)	42 (84)	.2	21 (23)	19 (21)	.4	5 (10)	7 (14)	.5
GG1	6 (13)	4 (8.0)		13 (14)	6 (6.7)		2 (4.1)	1 (2.0)	
GG2	5 (10)	4 (8.0)		30 (32)	31 (35)		19 (39)	19 (37)	
GG3	0 (0)	0 (0)		21 (23)	26 (29)		14 (29)	16 (31)	
GG4	3 (6.2)	0 (0)		2 (2.2)	4 (4.5)		5 (10)	1 (2.0)	
GG5	1 (2.1)	0 (0)		6 (6.5)	3 (3.4)		4 (8.2)	7 (14)	

Abbreviations: CTSBx, combined targeted and systematic biopsy; GG, Grade Group; PCa, prostate cancer; PIRADS, Prostate Imaging Reporting and Data System; TPLBx, targeted and perilesional biopsy.

therapeutic implications associated with TPLBx warrant further investigation. Furthermore, some limitations exist in TPLBx. Accurate characterization and 3-dimensional localization of lesion are crucial for precise TPLBx, which requires high level of expertise and MRI interpretation, making it not always be available worldwide. The operator variability should also be considered. The rapid development and application of AI may assist suspicious lesions localization, enhance the accuracy and accessibility.[16]

CONCLUSIONS

This RCT provides strong evidence supporting TPLBx as a valuable strategy for patients with a single unilateral suspicious lesion on prostate MRI. TPLBx achieves the noninferior GG $\geq$ 2-PCa diagnostic efficacy to CTSBx, and reduces complication rate, especially for bleeding-related complications. Compared with CTSBx, TPLBx significantly shortened the procedure time and saved the pathological examination cost. Further efforts are required to improve the standardization, validate these findings through large-scale, multicenter study, and finally promote the TPLBx scheme.

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