



# Comparison of combined MRI-TRUS fusion targeted and systematic biopsy vs systematic biopsy alone for the detection of prostate cancer in the Chinese biopsy-naïve patients: a prospective, single-center trial

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**Background:** This study aims to compare the combined MRI-TRUS fusion targeted biopsy (TB) and systematic biopsy (SB) vs SB for the detection of prostate cancer in Chinese biopsy-naïve patients suspected of prostate cancer.

**Methods:** This prospective study enrolled biopsy-naïve patients presenting from October 2020 to July 2024. Patients with PI-RADS scores  $\geq 3$  who met the inclusion criteria underwent transperineal TB combined with SB. Postoperative pathological data were collected from patients opting for radical prostatectomy at our institution. The primary outcome was the detection rate of clinically significant prostate cancer (csPCa) between combined biopsy and SB.

**Results:** A total of 644 biopsy-naïve patients participated, with 375 diagnosed with prostate cancer. Combined biopsy detected more csPCa cases compared to SB [316 (49.1%) vs 277 (43.0%), Absolute Risk Difference (ARD) 6.1% (95% CI: 4.2–7.9),  $P < 0.001$ ]. Exploratory subgroup analyses demonstrated that combined biopsy yielded significant benefits across most subgroups, particularly in patients with prostate-specific antigen density  $>0.15$  ng/ml and those with PI-RADS scores of 4–5. Among the 268 patients who underwent radical prostatectomy, the combined biopsy approach resulted in the lowest rate of postoperative pathological upgrading.

**Conclusions:** The combination of TB and SB demonstrates superior performance compared to SB alone in detecting csPCa in Chinese patients, with marked advantages observed in specific subgroups and a significant reduction in pathological upgrading following radical prostatectomy.

**Keywords:** clinically significant prostate cancer, MRI-targeted biopsy, systematic biopsy, transperineal biopsy

## Introduction

Prostate cancer (PCa) has become the most prevalent malignancy among men globally, with incidence rates continuing to rise<sup>[1]</sup>. Although the age-standardized incidence rate in China (9.81/

100 000) remains significantly lower than in European (59.9/100 000) and North American (73.5/100 000) populations<sup>[2,3]</sup>, its annual growth rate of 4.71% (95% CI: 3.12–9.95) reflects an escalating public health burden<sup>[4]</sup>. Chinese patients often present advanced stages with elevated prostate-specific antigen (PSA) levels<sup>[5,6]</sup>, likely due to limited screening access<sup>[7]</sup>. Furthermore, despite China's substantial population, there remains a critical gap in prospective studies that explore ethnic-specific

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carcinogenic profiles and optimized diagnostic strategies. Data from the California Cancer Registry reveal that Asian-American men of Chinese and Japanese descent exhibit poorer clinicopathological characteristics at diagnosis compared to other ethnic groups<sup>[8]</sup>. Genomic investigations have demonstrated distinct molecular alteration profiles in Chinese patients that markedly differ from Western cohorts<sup>[9]</sup>. Existing clinical guidelines predominantly depend on European and American population data, highlighting the urgent need for diagnostic frameworks tailored to the unique pathophysiological characteristics of Chinese populations.

Given the inherent heterogeneity of PCa, the treatment approaches are determined by an individual's risk profile<sup>[10]</sup>, making precise histological grading essential. The prevalence of indolent lesions among elderly males frequently leads to over detection of clinically insignificant prostate cancer (csPCa)<sup>[11]</sup>. Multiparametric MRI (mpMRI) has significantly improved PCa diagnosis, with sensitivity and specificity for clinically significant PCa (csPCa) ranging from 70% to 90%<sup>[12–15]</sup>. This technology enables precise lesion localization, facilitating targeted biopsy (TB), which detects csPCa more effectively than systematic biopsy (SB)<sup>[16–21]</sup>. However, relying solely on TB can still result in missing some csPCa, leading to treatment delays for certain patients. The retrospective study by Ahdoot *et al* shows that using TB alone would result in a missed diagnosis of 5.8% of csPCa cases<sup>[16]</sup>. Our published retrospective study indicates that performing only TB could overlook 5.5% of csPCa cases<sup>[22]</sup>. Despite this, the role of SB remains controversial. Stavriniades *et al* found that the overall survival rates for men with MRI-invisible Gleason 3 + 4 PCa were similar to those with Gleason 3 + 3<sup>[23]</sup>. In contrast, Kasivisvanathan *et al* argue that many studies overestimate the added value of SB due to design flaws. For instance, in many studies, operators performing systematic biopsies are typically aware of the location of MRI lesions, leading to biased targeting<sup>[24]</sup>. The added value of SB varies significantly across studies, ranging between 3% and 5%<sup>[17,22,24,25]</sup>.

This prospective study aims to assess the detection rates of combined biopsy and SB for csPCa. Biopsies were performed via the transperineal approach, which exhibits a well-documented safety profile in prior researches<sup>[26–28]</sup>. Furthermore, we establish gold-standard validation through correlation with radical prostatectomy specimens, enabling precise quantification of various biopsy methods.

## Patients and methods

### Study design and participants

The trial protocol has been previously published<sup>[29]</sup>. The trial was conducted at a public tertiary teaching hospital in China. Ethical approval has been obtained, and registration has been completed at the Chinese Clinical Trial Registry. This study has been reported according to STROCSS standards<sup>[30]</sup>.

Patients with elevated PSA levels who have not previously undergone a biopsy were invited to participate. Those meeting the inclusion criteria outlined in the research protocol were recruited and consented. Enrolled patients underwent both TB and SB. Participants were allowed to withdraw from the study at any time without providing a reason, and they continued with regular follow-up and treatment after withdrawal.

## HIGHLIGHTS

- Through a superiority-design framework, the study demonstrated that combined biopsy significantly outperforms systematic biopsy (SB) in detecting clinically significant prostate cancer (csPCa).
- The research utilized transperineal biopsy, addressing evidence gaps left by prior transrectal biopsy-dominant trials such as PRECISION and MRI-FIRST.
- The research employed self-comparison of subjects to evaluate the effects of combined targeted biopsy (TB) and SB versus SB alone, minimizing grouping bias while directly assessing SB's effectiveness in detecting mpMRI-visible lesions.
- Compared with radical prostatectomy specimens, combined biopsy showed significant reduction in postoperative pathological upgrading rates.

### Magnetic resonance imaging

All patients underwent 3.0 Tesla mpMRI following PI-RADS (v2.1) standards. The mpMRI sequence included T2-weighted imaging (T2 WI), dynamic contrast-enhanced imaging (DCE), and diffusion-weighted imaging with *b* values of 0, 100, 800, and 1500 s/mm<sup>2</sup>. Two uro-radiologists with expertise independently assessed visible lesions on mpMRI using PI-RADS v2.1. In cases of discrepant assessments, a third uro-radiologist was consulted to reach a consensus through joint review.

### Biopsy

Biopsies were performed by two urologists with over ten years of relevant experience. To minimize prostate bleeding and swelling caused by transrectal ultrasound (TRUS) biopsy, the biopsy will first conduct TB, followed by standard TRUS 12-core SB. The first urologist will perform 2–4 core biopsies for each lesion based on the foundation to ensure the accuracy of the TB. Meanwhile, the second urologist will perform the standard TRUS 12-core SB without MRI guidance. This approach effectively prevents the doctor from unintentionally or intentionally moving too close to lesions with PI-RADS scores (3–5) during the SB, ensuring the standardization and consistency of the biopsy. Urologists conducting the SB were specifically trained to disregard any signs of bleeding or other abnormalities.

### Histopathology and definition of clinical significance

Biopsy specimens were evaluated by two independent pathologists using the International Society of Urological Pathology (ISUP) 2019 grading criteria<sup>[31]</sup>. In cases of incongruity between the two outcomes, adjudication was carried out by a tertiary physician of superior rank. CsPCa was defined as an ISUP Gleason Grade (GG)  $\geq 2$  (Gleason score  $\geq 3 + 4$ ), while csPCa was strictly limited to GG1 (Gleason score  $3 + 3$ ). Downgrading is defined as any level of decline in postoperative pathological GG compared to biopsy pathology GG.

### Outcomes

The primary outcome of this study was the comparison of csPCa detection rates between combined biopsy and SB alone in patients with elevated PSA levels. The secondary outcomes encompass the

detection rates of cisPCa and the concordance between biopsy histopathology and radical prostatectomy pathology.

Adverse events

The adverse events in participants were monitored within 4 weeks after biopsy. Immediate postoperative assessment includes pain scoring using the visual analog scale. Telephone follow-ups at 24 hours and 4 weeks will document the complications, such as hematuria and urinary retention. If the participant undergoes prostatectomy within this period, the follow-up continues until the prostatectomy. Adverse events are graded according to the Common Terminology Criteria for Adverse Events (V.5.0), with grade ≥3 events requiring urgent intervention and reporting to the ethics committee within 24 hours.

Statistical analysis

The historical detection rate of csPCa via SB at our medical center was 32%<sup>[28]</sup>. Assuming a csPCa prevalence of 40% with combined biopsy, we have established the diagnostic equivalence test threshold at Δ + 5%, with a bilateral significance level (α) of 0.05 and a detection efficacy set at 0.80. Consequently, the final computed total of required patients amounts to 594 individuals.

We conducted data analysis using SPSS version 26 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were represented as frequencies and percentages. McNemar’s test was used to compare differences in csPCa detection between biopsy methods, with *P*-values adjusted for multiple comparisons using the Bonferroni correction. Statistical significance was defined as

*P* < 0.025 for the primary outcome and *P* < 0.004 for exploratory subgroup analysis. Inter-observer agreement was assessed using Conger’s kappa and Gwet’s agreement coefficient (AC). The adjusted Wald interval will be utilized to calculate confidence intervals (CIs) for cancer detection rates and to compare disparities in csPCa detection rates among SB and combined biopsy.

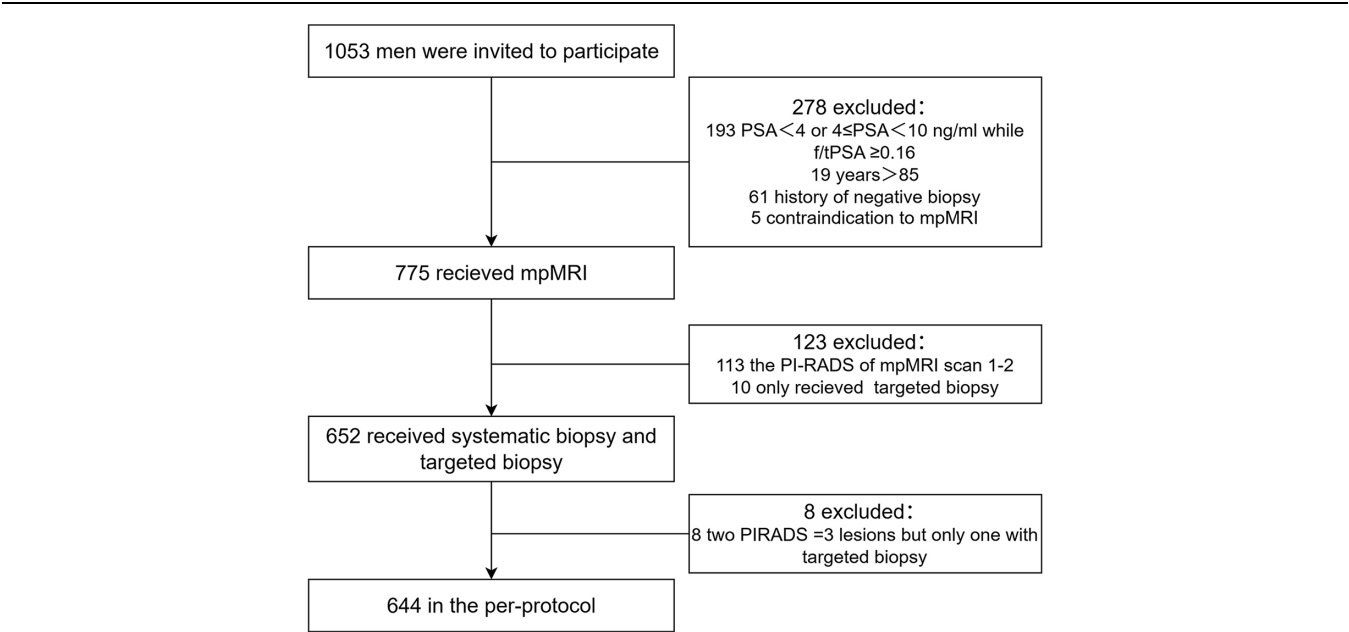
Results

Patient characteristics

A total of 644 patients who underwent their initial biopsy at our institution between October 2020 and July 2024 were recruited (Fig. 1). Table 1 presents the basic demographic information of the patients. The median age of the patients was 70 years, with a median PSA level of 13.3 ng/ml and a median prostate volume of 48 ml (Table 1). Of the patients, 37.0% exhibited PI-RADS 3 lesions, 38.2% had PI-RADS 4 lesions, and 24.8% had PI-RADS 5 lesions. Among those who underwent biopsy, 269 patients were diagnosed with benign disease, while 375 were diagnosed with PCa. Of the PCa patients, 268 underwent radical prostatectomy at our hospital.

Cancer detection rate

All patients underwent combined biopsy, with 375 diagnosed with PCa. The histological distribution of cancer cases was as follows: 9.2% were Gleason Grade (GG) 1, 10.7% were GG2, and 38.4% were GG3 or higher (Table 2). SB only identified 342 (53.1%) cases of PCa, of which 277 (43.0%) were csPCa. SB was used as a reference to compare the effectiveness of different biopsy methods. Both SB and TB demonstrated similar cancer



**Figure 1.** Research flowchart. This study initially invited 1053 male participants. Initially, 278 individuals were excluded: 193 cases due to PSA <4 ng/ml or PSA 4–10 ng/ml with free-to-total PSA ratio ≥0.16, 19 cases aged >85 years, and 5 cases contraindicated for mpMRI. The remaining 775 subjects underwent mpMRI, with 123 further excluded (113 cases with PI-RADS scores 1–2 and 10 cases receiving targeted biopsy only). Subsequently, 652 participants underwent concurrent systematic and targeted biopsies. 8 cases who had two PI-RADS = 3 lesions in the mpMRI were excluded due to the biopsy of only one lesion, leaving 644 fully protocol-compliant subjects for final inclusion in the per-protocol analysis. Inclusion criteria comprised: age 35–85 years; PSA ≥10 ng/ml or PSA 4–10 ng/ml with free/total PSA <0.16; PI- RADS of mpMRI scan 3–5; normal DRE or abnormal DRE with lesion confined to the prostate; informed consent, and complete diagnostic evaluation.

**Table 1**  
**Characteristics of the patients at baseline**

| Characteristic                                 | Total (n = 644)  |
|--|------------------|
| Age (y), median (IQR)                          | 70 (65–74)       |
| BMI (kg/m/m), median (IQR)                     | 24 (22–26)       |
| PSA (ng/ml)                                    |                  |
| Median (IQR)                                   | 13.3 (9.2–20.6)  |
| Maximum  | 479              |
| Prostate volume (ml)                           |                  |
| Median (IQR)                                   | 48 (35–70)       |
| Maximum  | 264              |
| PSA density(ng/ml <sup>2</sup> ), median (IQR) | 0.26 (0.17–0.47) |
| No. of cores of per person                     | 15.1 ± 1.1       |
| No. of cores on MRI-targeted biopsy per lesion | 2.9 ± 1.0        |
| PI-RADS score, n (%)                           |                  |
| 3  | 227 (37.0)       |
| 4  | 257 (38.2)       |
| 5  | 160 (24.8)       |

BMI, Body mass index; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen

detection rates, but TB identified more csPCa cases [300 (46.6%) vs 277 (43.0%); Absolute Risk Difference (ARD) 3.6% (95% CI: 1.3– 5.8),  $P = 0.003$ ], while reducing the detection of cisPCa [27 (4.2%) vs 65 (10.1%); ARD -5.9% (95% CI: -8.4 to -3.4),  $P < 0.001$ ]. Compared to SB alone, the combined TB and SB had detected more csPCa cases [316 (49.1%) vs 277 (43.0%); ARD 6.1% (95% CI: 4.2–7.9),  $P < 0.001$ ]. Adding SB to TB increased the detection of csPCa by 16 cases (2.5%), whereas incorporating TB into SB increased the detection of csPCa by 39 cases (6.1%; Fig. 2 and Table 2).

### Subgroup analyses

Subgroup analyses were conducted to evaluate the impact of clinical characteristics on PCa detection rates for SB versus combined biopsy. Results demonstrated significantly higher csPCa detection rates with combined biopsy across most subgroups (Table 3). Specifically, combined biopsy consistently outperformed SB in all strata of age, BMI, PSA levels, and prostate volume. For PSA density subgroups, combined biopsy showed superior detection when PSA density  $>0.15$  ng/ml<sup>2</sup> (56.1% vs 49.5%,  $P < 0.001$ ), while the difference did not reach statistical significance at PSAD  $\leq 0.15$  ng/ml<sup>2</sup> (21.4% vs 17.6%,  $P = 0.063$ ). Notably, detection rates were comparable between methods for PI-RADS category 3 lesions (7.9% vs 7.0%,  $P = 0.050$ ). The benefit of combined biopsy became increasingly pronounced with higher PI-RADS scores, reaching 90.6% (95% CI: 86.1–95.2) detection for PI-RADS 5 lesions.

### Association with radical prostatectomy

Among 375 patients diagnosed with PCa, 268 underwent immediate radical prostatectomy at our institution. The three biopsy methods were compared based on the postoperative pathological findings of patients who subsequently underwent radical surgery (Fig. 3). Among the patients who were diagnosed via SB, 44.6% experienced pathological upgrading after surgery, with 20.5% advancing from cisPCa to csPCa. The upgrading rate was lower for TB compared to SB. After the

**Table 2**  
**Detection of clinically significant prostate cancer**

|  | MRI-targeted | Systematic | Combined   |
|--|--------------|------------|------------|
| Biopsy ISUP grade group, n (%)   |              |            |            |
| Benign   | 317 (49.2)   | 302 (46.9) | 269 (41.8) |
| 1  | 27 (4.2)     | 65 (10.1)  | 59 (9.2)   |
| 2  | 72 (11.2)    | 63 (9.8)   | 69 (10.7)  |
| 3  | 78 (12.1)    | 59 (9.2)   | 68 (10.6)  |
| 4  | 106 (16.5)   | 106 (16.5) | 121 (18.8) |
| 5  | 44 (6.8)     | 49 (7.6)   | 58 (9)     |
| Detection rate for PCa, n (%)  | 327 (50.8)   | 342 (53.1) | 375 (58.3) |
| Detection rate for csPCa, n (%)  | 300 (46.6)   | 277 (43.0) | 316 (49.1) |
| Additional grade group $\geq 2$ cancer diagnosis by biopsy method, n (%) | 39 (6.1)     | 16 (2.5)   |            |
| New grade group 1 cancer diagnosis by biopsy method, n (%)               | 12 (1.9)     | 36 (5.6)   |            |

csPCa, Clinically significant prostate cancer; ISUP, International Society of Urological Pathology; MRI, magnetic resonance imaging

combined biopsy, 29.7% of patients showed pathological upgrading, with 10.2% upgrading to csPCa. The overall pathological upgrading rate in combined biopsy (29.7%) was lower than that seen with either SB (29.7% vs 44.7%,  $P < 0.001$ ) or TB (29.7% vs 40.6%,  $P = 0.015$ ). In terms of downgrading, the risk of reducing to cisPCa after surgery was minimal across all three biopsy methods, with the combined biopsy showing the highest downgrading rate (Fig. 3). Overall, the combined biopsy had the highest postoperative concordance rate, which was significantly higher compared to SB (47.6% vs 37.0%,  $P = 0.014$ ). Among the remaining 107 patients, 51 underwent endocrine-based therapy following biopsy, while 32 elected surgical treatment at an external institution (Supplemental Digital Content Table 1, available at: <http://links.lww.com/JS9/F574>).

### Inter-observer agreement in MRI readers

Initial PI-RADS scores were identical between both radiologists in 82.3% (Gwet's AC = 0.78) of all cases. The inter-observer agreement yielded a kappa value of 0.73 for PI-RADS assessments, indicating substantial consistency (Supplemental Digital Content Table 2, available at: <http://links.lww.com/JS9/F574>).

### Inter-observer agreement in histopathologic readers

In the SB group, the agreement rate for GG was 84.5% (Gwet's AC = 0.82) (Supplemental Digital Content Table 3, available at: <http://links.lww.com/JS9/F574>), while in the TB group, the GG agreement rate was also 85.7% (Gwet's AC = 0.83) (Supplemental Digital Content Table 4, available at: <http://links.lww.com/JS9/F574>).

### Adverse events

Adverse events associated with the biopsy are rare, with the most common being hematuria, occurring in 11.3% of cases. Infections are extremely uncommon (0.6%). Transient exacerbation of urinary retention symptoms was observed in 2% of

|   | No. of Patients in Grade Group with Targeted Biopsy |        |    |    |    |     |    | Total |
|---|---|--------|----|----|----|-----|----|-------|
|   |   | Benign | 1  | 2  | 3  | 4   | 5  |       |
| No. of Patients in Grade Group with Systematic Biopsy | Benign  | 269    | 12 | 10 | 5  | 3   | 3  | 302   |
|   | 1   | 36     | 11 | 12 | 3  | 2   | 1  | 65    |
|   | 2   | 5      | 2  | 39 | 13 | 3   | 1  | 63    |
|   | 3   | 3      | 1  | 9  | 35 | 11  | 0  | 59    |
|   | 4   | 4      | 1  | 2  | 22 | 73  | 4  | 106   |
|   | 5   | 0      | 0  | 0  | 0  | 14  | 35 | 49    |
| Total   |   | 317    | 27 | 72 | 78 | 106 | 44 | 644   |

Upgrading by systematic biopsy

Concordant

Upgrading by targeted biopsy

Figure 2. Cross-tabulation of systematic biopsy and targeted biopsy.

cases following biopsy. Follow-up showed that the majority of adverse events resolved spontaneously over time. No severe adverse events (grade 3 or higher) were observed among the enrolled patients.

Discussion

This is the largest prospective study in China comparing the combined MRI-TRUS fusion TB and SB vs SB alone for the detection of PCa in biopsy-naïve patients. Our research delineates a substantial increase in csPCa detection rates via combined biopsy [316 (49.1%) vs 277 (43.0%), ARD 6.1% (95% CI: 4.2–7.9),  $P < 0.001$ ], concurrently reducing the detection of cisPCa. This study made a series of methodological optimizations during its design. Firstly, we employed a superiority design with a 5% threshold, demonstrating that combined biopsy is a more effective biopsy approach compared to SB. Secondly, this study evaluated

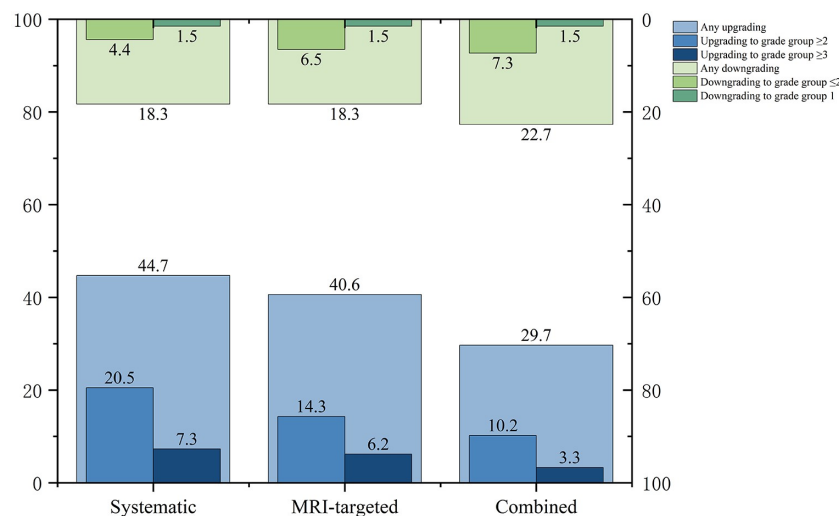
the diagnostic results of SB and TB within the same patient cohort, which effectively reduced selection bias and clarified the additional diagnostic value of each method. In addition, all participants in our study underwent transperineal biopsy. A prior prospective controlled trial from our institution demonstrated that transperineal biopsy significantly reduced the incidence of major complications (including hyperthermia) compared to transrectal biopsy (0.6% vs 4.3%,  $P < 0.001$ )<sup>[28]</sup>. Notably, pre-existing large-scale trials such as MRI-FIRST and PRECISION, initiated before our research, employed the transrectal approach<sup>[18,32]</sup>. Owing to its superior safety profile and reduced postoperative complications, transperineal biopsy is now internationally endorsed as the gold-standard technique for PCa diagnosis<sup>[26,27]</sup>. Due to its simplicity and feasibility, SB has traditionally served as the predominant biopsy methodology for diagnosing PCa over the past several decades<sup>[33]</sup>. However, its broad biopsy scope often leads to a high detection rate of cisPCa<sup>[34]</sup>. The emergence of TB has optimized this scenario, with multiple studies demonstrating

Table 3  
Detection rates of csPCa by subgroup

| Characteristic           | N   | MRI-targeted      | Systematic          | Combined          | P <sup>a</sup> |
|--------------------------|-----|-------------------|---------------------|-------------------|----------------|
| Age                      |     |                   |                     |                   |                |
| Years≤70                 | 354 | 39.5% (34.4–44.7) | 35.3% (30.3–40.3)   | 41.5% (36.4–46.7) | <0.001         |
| Years>70                 | 290 | 55.2% (49.4–60.9) | 52.4% (46.6–58.2)   | 58.3% (52.6–64.0) | <0.001         |
| BMI                      |     |                   |                     |                   |                |
| ≤24 kg/m <sup>2</sup>    | 344 | 45.3% (40.1–50.6) | 41.0% (35.8–46.2)   | 47.4% (42.1–52.7) | <0.001         |
| >24 kg/m <sup>2</sup>    | 300 | 48.0% (42.3–53.7) | 45.3% (39.7–51.0)   | 51.0% (45.3–56.7) | <0.001         |
| PSA                      |     |                   |                     |                   |                |
| ≤10 ng/ml                | 182 | 41.8% (34.5–49.0) | 34.6% (27.6–41.6)   | 45.6% (38.3–52.9) | <0.001         |
| >10 ng/ml                | 462 | 48.5% (43.9–53.1) | 46.3% (41.8–50.9)   | 50.4% (45.9–55.0) | <0.001         |
| Prostate volume          |     |                   |                     |                   |                |
| ≤50 ml                   | 338 | 66.6% (61.5–71.6) | 60.7% (55.4–65.9.6) | 68.9% (64.0–73.9) | <0.001         |
| >50 ml                   | 306 | 24.5% (19.7–29.4) | 23.5% (18.7–28.3)   | 27.1% (22.1–32.1) | <0.001         |
| PSA density              |     |                   |                     |                   |                |
| ≤0.15 ng/ml <sup>2</sup> | 131 | 16.8% (10.3–23.3) | 17.6% (11.0–23.3)   | 21.4% (14.3–28.5) | 0.063          |
| >0.15 ng/ml <sup>2</sup> | 513 | 54.2% (49.9–58.5) | 49.5% (45.2–53.9)   | 56.1% (51.8–60.4) | <0.001         |
| PI-RADS score            |     |                   |                     |                   |                |
| 3                        | 227 | 4.8% (2.0–7.7)    | 7.0% (3.7–10.4)     | 7.9% (4.4–11.5)   | 0.050          |
| 4                        | 257 | 56.8% (50.7–62.9) | 49.8% (43.7–56.0)   | 59.5% (53.5–65.6) | <0.001         |
| 5                        | 160 | 89.4% (84.5–94.2) | 83.1% (77.3–89.0)   | 90.6% (86.1–95.2) | <0.001         |

<sup>a</sup>Combined vs Systematic biopsy; A  $P$ -value of less than 0.004 was considered to indicate statistical significance with the use of the Bonferroni correction  
Data are % (95% CI).  
BMI, body mass index; csPCa, clinically significant prostate cancer; PSA, prostate-specific antigen; PI-RADS, Prostate Imaging Reporting and Data System





**Figure 3.** Upgrading and downgrading of cancer grade group after whole-mount histopathological analysis.

its ability to enhance csPCa detection while reducing overdiagnosis of cisPCa<sup>[16,17,32,35,36]</sup>. Our study corroborates these findings, showing a 3.6% higher detection rate of csPCa in TB than in SB. However, relying exclusively on TB presents limitations. PCa is inherently heterogeneous and multifocal<sup>[37]</sup>, and certain rare cancer types associated with high-grade cancer, such as intraductal carcinoma, may be invisible on MRI due to their unique characteristics<sup>[38,39]</sup>. Our study further highlights that TB alone could result in the missed diagnosis of 2.5% of csPCa cases. Thus, combined biopsy emerges as a more comprehensive and precise diagnostic strategy. Exterkate *et al* demonstrated that using combined biopsy can increase the detection rate of PCa by 6%<sup>[35]</sup>. Similarly, the GÖTEBORG-2 trial revealed that SB had a higher likelihood of diagnosing cisPCa compared to combined biopsy (21% vs 20%)<sup>[17]</sup>. Our study further revealed that combined biopsy increased csPCa detection by 6.1% while reducing cisPCa diagnoses by 0.9% compared to SB alone. Combined biopsy reduced the risk of pathological upgrading (particularly for misclassification of csPCa) and demonstrated higher diagnostic concordance compared to SB (47.6% vs 37.0%,  $P = 0.014$ ). These results are also consistent with the conclusions of previous studies and provide important evidence for improving the preoperative risk stratification in the management of PCa<sup>[40]</sup>.

Subgroup analysis further highlighted the superior diagnostic performance of combined biopsy over SB alone in detecting csPCa, particularly within high-risk subgroups, supporting a risk-stratified, individualized biopsy strategy. Specifically, the PSA range of <10 ng/ml is often considered a diagnostic gray zone<sup>[41]</sup>. In this range, patients are more likely to present with smaller lesions and subtle or absent clinical symptoms, and are less likely to be detected via digital rectal examination<sup>[42,43]</sup>, thus underscoring the need for advanced screening methods. Li *et al* demonstrated that MRI-based radiomics can effectively identify lesions within the PSA 4–10 ng/ml range<sup>[44]</sup>, while Lee *et al* confirmed that TB enhances the detection rate of csPCa in patients with PSA levels <10 ng/ml<sup>[45]</sup>, supporting the advantages of our combined biopsy approach. Concurrently, this study observed lower csPCa incidence in patients with large prostate volumes, potentially related to benign hyperplasia suppressing tumor

invasiveness<sup>[46,47]</sup>. Meanwhile, PSA density (PSAD) – an indicator of tumor burden per unit volume – showed positive correlation with malignancy risk. Arafa *et al*'s study found that compared to SB, PSAD has a higher area under the curve (AUC: 0.77 vs 0.73) in TB<sup>[48]</sup>. PSAD serves as a stratification tool to refine biopsy strategies. Notably, research by Ahdoot *et al* revealed that in patients with PSAD  $\geq 0.2$  ng/ml<sup>2</sup>, SB provides only a marginal 2% incremental csPCa detection (95% CI: 0.4%–5.9%), suggesting SB may be safely omitted in this subgroup<sup>[49]</sup>. Regarding imaging stratification, PI-RADS scoring served as the core guidance tool: for PI-RADS category 3 lesions, our study showed that TB alone detected only 4.8% of csPCa (95% CI: 2.0%–7.7%), which increased to 7.9% (95% CI: 4.4%–11.5%) with the addition of SB. This aligns with the finding by Brisbane *et al*<sup>[50]</sup> that 90% of csPCa lesions extend beyond 16 mm<sup>2</sup>, supporting extensive sampling for such intermediate-risk lesions. The PI-RADS subgroup analysis by Jiang Xingkang *et al* revealed that in the PIRADS 4 score, saturated biopsy significantly outperformed SB in detecting csPCa (100% vs 74.4%,  $P < 0.001$ )<sup>[51]</sup>. Ahdoot *et al*'s results also indicate that in cases with PI-RADS scores of 3–4, the addition of SB significantly improves the detection rate of csPCa, while the benefit for patients with a PI-RADS score of 5 is minimal<sup>[52]</sup>. Similarly, Noh *et al* observed that SB provided only a marginal incremental diagnostic value (0.7%) for csPCa detection in PI-RADS 5 cases<sup>[53]</sup>. Our findings revealed that TB and combined biopsy demonstrated near-perfect agreement ( $\kappa = 0.931$ ) in detecting csPCa for PI-RADS category 5 lesions. This high level of concordance suggests that omitting systematic biopsies may be a feasible approach when PI-RADS 5 lesions are identified. Therefore, integrating risk stratification parameters, including PI-RADS scores and PSAD, with emerging techniques such as artificial intelligence-guided TB could facilitate personalized biopsy strategies, thereby improving diagnostic precision<sup>[54,55]</sup>.

Despite the demonstrated superiority of combined biopsy in csPCa detection, the consequential risk of overdiagnosis remains a critical clinical consideration. Our study found that 22.7% of patients who underwent combined biopsy experienced downgrading after radical prostatectomy, with 7.3% showing a reduction to Gleason grade 2. These findings are consistent

with the results of Sorce *et al*<sup>[56]</sup>. Notably, smaller lesions ( $\leq 10$  mm) carry the highest downgrading risk (18% vs 14% for larger tumors)<sup>[57]</sup>, potentially leading to overtreatment if biopsy grading alone guides management. Given the indolent nature of PCa (2.7% cancer-specific mortality at 10 years in ProtecT)<sup>[58]</sup>, and safety of active surveillance for low-intermediate risk disease ( $GG \leq 2$ )<sup>[58–60]</sup>, biopsy-induced downgrading may lead to overtreatment. Most upgrading cases are low-risk, with minimal effect on prognosis<sup>[61]</sup>. Therefore, Clinicians must carefully weigh the potential for downgrading when using combined biopsy, particularly for small lesions. In addition, the perilesional biopsy recommended by the European Association of Urology guidelines may help reduce the risk of postoperative upstaging, although the results still require verification through prospective studies<sup>[62]</sup>.

In terms of adverse events, our findings are consistent with other studies<sup>[20,63,64]</sup>. Some studies have shown that the use of anticoagulants prior to transperineal biopsy does not increase the risk of bleeding<sup>[65]</sup>. The low incidence of infection and hematuria may be attributed to the prophylactic use of antibiotics and selection of the transperineal approach<sup>[28]</sup>.

Undeniably, our study has certain limitations. Firstly, it was conducted at a single center, which may affect the generalizability of its findings. Secondly, our study included patients with PSA levels between 4 and 10 and a free-to-total PSA ratio  $< 0.16$ , meaning our findings may not apply to those with a higher ratio. Thirdly, the actual detection rates for csPCa were 43.0% for SB and 49.1% for combined biopsy, both higher than the rates assumed in our original sample size calculation. That calculation was based on institutional data from 2015<sup>[28]</sup>, before mpMRI became routine, whereas our cohort consisted exclusively of men with PI-RADS scores of 3 or higher. Although the observed difference in detection rates between biopsy methods was 6.1%, slightly lower than the 8% used for power calculation, the difference remained statistically significant and strongly supports our primary outcome. Fourthly, bleeding and edema induced by targeted biopsies could potentially influence the accuracy of subsequent systematic biopsies. To mitigate this sequence-related bias, operators were required to perform SB based solely on anatomical landmarks rather than visual cues from bleeding or tracts. Nevertheless, the technical influence of prior biopsies cannot be entirely eliminated. Additionally, we only collected postoperative histological data from patients who underwent radical prostatectomy at our institution. However, not all patients received surgery or were treated at our institution, which could introduce selection bias in the radical prostatectomy pathology.

In conclusion, our prospective study highlights the value of the combined biopsy technique as a promising approach for detecting csPCa. The results support the integration of combined MRI-TRUS fusion TB and SB for the detection of prostate cancer in Chinese biopsy-naïve patients. However, determining the optimal biopsy strategy for individual patients warrants further multicenter studies and long-term clinical follow-up to ensure a comprehensive evaluation.

## Ethical approval

Ethical approval for this study was obtained from the relevant ethics committee.

## Consent

Written informed consent was obtained from the patient.

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## Author contributions

B.Y., X.Y., and B.S.: conceptualization; A.K., C.T., D.S., Y.H., G.X., and C.G.: resources; W.L. and A.K.: investigation; C.T., D.S., Y.H., K.Z., B.Z., S.M., D.H., and C.G.: data curation; W.L., B.Y., and A.K.: formal analysis; W.L. and A.K.: writing – original draft; B.Y. and Q.W.: writing – review & editing; B.Y. and B.S.: supervision; B.Y., B.S., and Q.W.: project administration; B.Y. and B.S.: funding acquisition.

## Conflicts of interest disclosure

No conflict of interest exists.

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## Data availability statement

Research data can be obtained from the corresponding author through reasonable requests.

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