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Original Article

Comparison between ^{18}F-DCFPyL PET/MRI-guided ultrasound fusion targeted biopsy and systematic biopsy for tumor detection and grading in selected patients: A prospective randomized controlled trial

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KEYWORDS
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Abstract *Objective:* This study aimed to compare the upgrade rate and cancer detection rate between the ^{18}F-DCFPyL PET/MRI-guided ultrasound fusion targeted biopsy (TB) and systematic biopsy in selected patients with suspected prostate cancer (the molecular imaging prostate-specific membrane antigen score of $\geq$2 and multiparametric MRI Prostate Imaging Reporting and Data System score of $\geq$4).
Methods: Eighty-seven selected biopsy-naive patients were randomized into two groups: TB (n=41) and systematic biopsy (control; n=46). Patients diagnosed with clinically significant prostate cancer proceeded to radical prostatectomy. The primary outcome was the pathological upgrade rate. Secondary outcomes, including the cancer detection rate, incidence of repeat biopsy, positive surgical margin, complications, and prostate-specific antigen level at 6 weeks postoperatively, were compared between the groups using the Pearson or Fisher's exact test, as appropriate.

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Results: In the study, prostate cancer was ultimately detected in all patients. The TB group successfully identified all tumors, whereas five patients in the control group initially missed diagnosis. The pathological upgrade rates for the TB and control groups were 31.7 % and 56.5%, respectively. Overall, the detection rate for clinically significant prostate cancer (the International Society of Urological Pathology grade of $\geq$2) was significantly higher in the TB group (92.7%) compared with the control group (76.1%, p=0.035). However, no significant difference was found in the detection rate of all prostate cancer. Complications (Clavien–Dindo grade of $\leq$2) occurred in both the TB group (n=11) and control group (n=13). No statistically significant difference was observed between the groups in terms of the positive surgical margin, complications, or 6-week postoperative prostate-specific antigen level.
Conclusion: The ^{18}F-DCFPyL PET/MRI-guided ultrasound fusion TB alone was an efficient modality in diagnosing selected patients with prostate cancer.

1. Introduction

Prostate cancer (PCa) is the second most common malignancy worldwide and the fifth leading cause of cancer-related mortality among men [1]. Currently, the treatment selection for PCa depends on the biopsy results as different preoperative histological profiles affect the operative strategy [2].

The traditional 12-core systematic biopsy (SB, control group) is commonly employed for the diagnosis and grading of PCa; however, its limitation in missed detection and grading misclassification has been widely reported [3]. In contrast, the PET/MRI-guided targeted biopsy (TB) has been shown to enhance the detection rate for clinically significant PCa (csPCa). Notably, the TB has been associated with a miss rate of 14% for csPCa [4] and can result in a pathological upgrade of the Gleason score (GS) by 30.9% [5]. Consequently, a combined biopsy approach is recommended for biopsy-naive patients with suspicious lesions. Nevertheless, this approach, which involves a greater number of cores, can potentially lead to increased complications and patient anxiety [6,7].

Prostate-specific membrane antigen (PSMA) PET/MRI, combining the advantages of multiparametric MRI (mpMRI) and PSMA PET, is a promising modality for guiding a biopsy with demonstrated feasibility [8]. The prospective single-arm paired comparison study [9] showed that mpMRI outperformed PSMA-PET/CT in identification of PCa, although the distinction was not notable when detecting csPCa. The synergy of mpMRI and PSMA-PET/CT demonstrated enhanced sensitivity and negative predictive value (NPV) [9]. Similarly, the PRIMARY study underscored the superior NPV and sensitivity of the combined approach for detecting csPCa [10]. In our previous trial, all patients with a score of 4 on PET/MRI (the molecular imaging PSMA [miPSMA] score of $\geq$2 and Prostrate Imaging Reporting and Data System [PI-RADS] score of $\geq$4) were diagnosed with PCa followed its guided TB [11]. However, few prospective studies have assessed the value of PSMA PET/MRI-guided TB in detection of PCa. This study aimed to address this research gap by examining the efficacy of PSMA PET/MRI-guided TB for detecting PCa in a selected patient population.

2. Patients and methods

2.1. Design

This study is a prospective single-centre randomized controlled trial (RCT) that evaluates the cancer detection rate, csPCa detection rate, and accuracy of pathology Gleason grading between PSMA PET/MRI-guided TB and SB in selected patients. This study was approved by the local regional committee in the First Medical Centre of the PLA General Hospital (S2021-565-01) for medical and health ethics and the study was registered on the Chinese Clinical Trial Registry (ChiCTR2100053310).

2.2. Study population

Overall, 87 patients were enrolled between January 2021 and January 2022, all of whom provided the written informed consent. Before enrolment, all participants suspected of PCa through digital rectal examination or serum prostate-specific antigen (PSA) screening underwent PET/MRI examination (^{18}F-DCFPyL was chosen as the PSMA radioligand). The scanner, parameters, and procedure of the examination have been described previously [11]. The results were independently evaluated by two experienced nuclear medicine physicians (Liu Y and Xu B) and scored ranging from 1 to 4 according to the standardized evaluation as our previous research [11]. Additionally, each suspected prostate lesion was assigned a miPSMA score [12] and PI-RADS score using the PI-RADS v2.1 method [13].

The inclusion criteria were as follows: patients with a PSMA PET/MRI score of 4 (PI-RADS score of $\geq$4 and miPSMA score of $\geq$2), miPSMA score of 2 determined to be equal to or above the uptake of liver and lower than parotid gland, age of 50–80 years old, and PSA level from 4 ng/mL to 30 ng/mL. The exclusion criteria were as follows: inability to tolerate a biopsy or radical prostatectomy (RP), previous radiation or hormone therapy, previous biopsy or trans-

urethral resection of the prostate, or evidence of metastasis. The withdrawal criteria were as follows: refusal of surgical treatment after diagnosis or could not complete the follow-up visit.

Participants were randomly allocated to the TB and SB groups in 1:1 ratio using a web-based statistical software (https://spssau.com/). Given the obvious differences in the number of cores between the groups, the group allocation was not masked from the surgeons and patients. A flow diagram for the study is shown in Fig. 1.

2.3. Intervention

Patients with a PSMA PET/MRI score of 4 received 2–4-core PSMA PET/MRI-guided ultrasound fusion TB and standard 12-core SB, respectively [11]. The number of cores was determined by the surgeons based on their satisfaction with the obtained samples. If the primary biopsy was negative, a repeated biopsy was performed using the opposite approach. All biopsies were performed under local anesthesia in the outpatient clinic by an experienced urologist (Niu S). The BK predictive fusion prostate biopsy system and software (BK Medical Technology Shanghai Co., Ltd, Shanghai, China) were used for PET/MRI-guided ultrasound fusion TB. The procedure of performing TB was the same as the previous report [11]. Patients with csPCa underwent robot-assisted RP.

Clinical characteristics, including the age, body mass index, serum PSA level, prostate volume, and ratio of free PSA to total PSA (f/tPSA) were collected before the biopsy. Prostate specimens were analyzed by two experienced pathologists. The Gleason grading system was promoted in 2014 by the International Society of Urological Pathology (ISUP) [14]. The PCa, prostatic intraepithelial neoplasia or inflammation, GS, and size of lesions were assessed. Surgical margins for postoperative specimens were also evaluated. A follow-up visit was scheduled at 6 weeks postoperatively and the PSA level was measured.

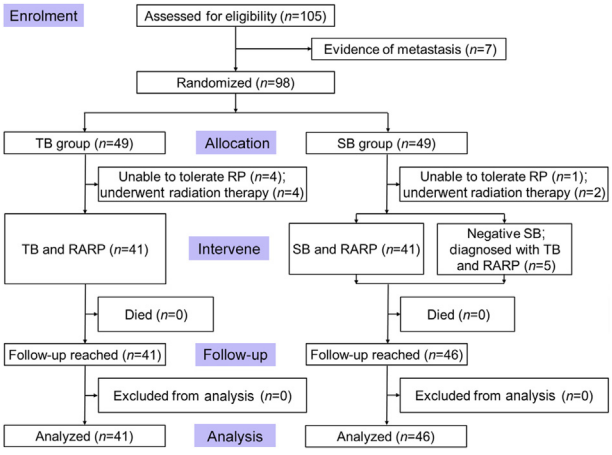

Figure 1 The flow diagram of this trial. SB, systematic biopsy; TB, targeted biopsy; RP, radical prostatectomy; RARP, robot-assisted RP.

2.4. Outcomes

The primary outcome was the pathological upgrade rate. An upgrade was defined as a higher GS in the RP specimen compared to the biopsy samples. In cases where patients had multifocal lesions, only the dominant lesion, as determined by volume, was considered for an analysis.

The secondary outcomes included the PCa detection, repeat biopsy incidence, positive rate, complications after a biopsy, positive surgical margin (PSM), and PSA level at 6 weeks postoperatively. PCa detection included PCa and csPCa; the latter was defined as a tumor with the ISUP grade of $\geq$2. A PSM was the portion of the tumor found at the inked margin of the postoperative specimen [15]. Complications after a biopsy were evaluated using the Clavien–Dindo classification [16].

2.5. Statistical analysis

For our previous research outcome [11], assuming the upgrade rate in the TB and SB groups to be 25% and 55%, respectively [5], we needed 38 patients in each group for a 5% (one-sided) significance level and 80% power to verify the conclusion. We accepted a 5% loss to follow-up and deemed 40 participants in each group as sufficient.

Quantitative variables are described as mean, standard deviation, maximum, minimum, median, and interquartile range, and categorical variables are described by numbers and percentages. Differences in cancer detection, repeat biopsy incidence, positive repeat biopsy, and pathological upgrade rates between the targeted and control groups were compared using the Pearson or Fisher's exact tests as appropriate. An independent-sample *t*-test and the Mann–Whitney *U* test were used to assess differences in quantitative variables after testing the distribution for normality. Data were analyzed using SPSS v.26.0 (IBM Corp, Armonk, NY, USA). The statistical significance was set at $p<0.05$.

3. Results

3.1. Participants

Eligible patients ($n=87$) were randomized to the TB and SB groups. There was no difference in the age, body mass index, PSA level before a biopsy, prostate volume, or other clinical characteristics between the two groups (Table 1). The number of patients who withdrew from the study (with reasons for withdrawal) are presented in Fig. 1.

3.2. Histopathologic characteristics of postoperative specimens and the follow-up visit

As shown in Table 2, all patients had PCa. No significant difference was noted in the ISUP grade between the groups for postoperative specimens ($p=0.089$). Compared with the SB group, the TB group had a lower pathological upgrade rate (31.7% *vs.* 56.5%, $p=0.020$). However, there was no difference between the groups in terms of the PSM ($p=0.9$). At 6 weeks postoperatively, 5 (12.2%) and 2 (4.3%) patients in the TB group and SB group, respectively, had the PSA level of $\geq$0.1 ng/mL ($p=0.4$).

Table 1 Demographic characteristics of study patients.

Variable	Overall	TB group	SB group	*p*-Value*
Patient, *n*	87	41	46	Not available
Age, mean±SD, year	68.2±7.2	68.9±7.9	67.7±6.6	0.4
BMI, mean±SD, kg/m^2	25.0±2.6	24.6±2.4	25.4±2.6	0.15
tPSA, median (IQR), ng/mL	9.11 (6.26, 16.71)	8.72 (5.94, 14.74)	11.57 (7.05, 17.10)	0.12
fPSA, median (IQR), ng/mL	1.09 (0.71, 1.61)	1.15 (0.67, 1.59)	1.01 (0.71, 1.66)	0.8
f/tPSA, median (IQR)	0.10 (0.08, 0.16)	0.11 (0.08, 0.17)	0.10 (0.08, 0.14)	0.3
PV, median (IQR), mL	36.4 (27.3, 49.3)	37.9 (26.7, 58.3)	35.2 (27.9, 48.4)	0.6

TB, targeted biopsy; SB, systematic biopsy; SD, standard deviation; BMI, body mass index; PSA, prostate-specific antigen; tPSA, total PSA; fPSA, free PSA; f/tPSA, the ratio of fPSA to tPSA; PV, prostate volume; IQR, interquartile range.
* The values were from the comparison between the TB and SB groups.

3.3. Histopathologic characteristics of biopsies and complications

The histopathologic biopsy characteristics and complications for both groups are shown in Table 3. A significant difference in the csPCa detection rate was observed between the TB and SB groups ($p=0.035$) and no significant difference was found in the total PCa detection rate ($p=0.087$). No significant difference was found in the ISUP grade between the two groups ($p=0.16$). No serious perioperative complications (Clavien–Dindo grade of >2) occurred after the biopsy in either group.

3.4. Repeat biopsy

No patients in the TB group underwent the repeat biopsy, whereas five patients in the SB group underwent repeat biopsy. Table 4 shows the five patients' characteristics, which included the PSA, PSAD, tumor volume, and lesion's location. Using the 12-region sectors of the prostate reporting scheme (left or right, anterior or posterior, and base, middle or apex) [17], four patients with cancerous lesions in the anterior regions were missed in the initial diagnosis. Fig. 2 shows the results of PSMA PET/MRI images and the specimens postoperatively of one patient.

4. Discussion

An optimal prostate biopsy should be characterized by high accuracy, minimal invasiveness, and a low incidence of complications. In this study, all patients with a score of 4 on PSMA PET/MRI were successfully diagnosed as PCa through TB alone, experiencing a lower rate of pathological upgrade.

Compared with the SB, the TB demonstrated an increased detection rate for high-risk PCa [18]. Moreover, the strategy of utilizing MRI for risk assessment prior to a biopsy, followed by the TB, has been proven to outperform

Table 2 Intraoperative variables and histopathologic characteristics of postoperative specimens and the follow-up visit.

Variable	TB group (*n*=41)	SB group (*n*=46)	*p*-Value
Operative time, median (IQR), min	120 (110, 150)	134 (110, 173)	0.001
Blood loss, median (IQR), mL	50 (50, 100)	75 (50, 100)	0.11
Nerve sparing, *n* (%)			0.8
No	24 (58.5)	30 (65.2)	
Lateral	8 (19.5)	8 (17.4)	
Bilateral	9 (22.0)	8 (17.4)	
Detection, *n* (%)			0.5
Overall cancer	41 (100)	46 (100)	
csPCa	41 (100)	45 (97.8)	
ISUP grade, *n* (%)			0.089
1	0	1 (2.2)	
2	13 (31.7)	6 (13.0)	
3	13 (31.7)	15 (32.6)	
4	12 (29.3)	13 (28.3)	
5	3 (7.3)	11 (23.9)	
Upgrade, *n* (%)	13 (31.7)	26 (56.5)	0.020
PSM, *n* (%)	14 (34.1)	15 (32.6)	0.9
PSA in a 6-week follow-up visit			
<0.02 ng/mL	26 (63.4)	37 (80.4)	0.070
≥0.1 ng/mL	5 (12.2)	2 (4.3)	0.4

TB, targeted biopsy; SB, systematic biopsy; csPCa, clinically significant prostate cancer; ISUP, the International Society of Urological Pathology; PSM, positive surgical margin; PSA, prostate-specific antigen; IQR, interquartile range.
Note: percentages may not add up to 100% due to rounding.

Table 3 Histopathologic characteristics and complications of biopsy.

Variable	TB group (n=41)	SB group (n=46)	p-Value
Total core (core per patient), n	134 (3.3)	552 (12.0)	NA
Total positive core (positive core per patient)	120 (2.9)	211 (4.6)	
Detection, n (%)			
Overall cancer	41 (100)	41 (89.1)	0.087
csPCa	38 (92.7)	35 (76.1)	0.035
ISUP grade, n (%)			0.16
No cancer	0	5 (10.9)	
1	3 (7.3)	6 (13.0)	
2	15 (36.6)	9 (19.6)	
3	12 (29.3)	13 (28.3)	
4	7 (17.1)	10 (21.7)	
5	4 (9.8)	3 (6.5)	
Clavien–Dindo graded complication, n (%)	11 (26.8)	13 (28.3)	1
Grade 1	7 (17.1)	9 (19.6)	
Grade 2	4 (9.8)	4 (8.7)	
Grade >2	0	0	

TB, targeted biopsy; SB, systematic biopsy; ISUP, the International Society of Urological Pathology; csPCa, clinically significant prostate cancer; NA, not available.
Note: percentages may not add up to 100% due to rounding.

the SB [19]. Nonetheless, the TB alone was found to still miss the detection of certain tumors while the combined SB resulted in a higher detection rate of PCa [4,5]. In addition, an increased number of biopsy cores may lead to more complications, such as urinary tract infection, bleeding, hematuria, and lower urinary tract symptoms [6,7]. When compared to mpMRI (PI-RADS≥3), ^{68}Ga-PSMA PET/CT has demonstrated a better diagnostic accuracy as a stand-alone procedure for the diagnosis and staging of high-risk PCa [20]. Its ability of detecting malignancy and accurately identifying csPCa in patients with high suspicion of cancer on mpMRI was also verified in patients with a previous negative biopsy. On the other hand, the role of PET/CT in excluding tumors is similarly valuable. One study discussed the NPV of PSMA in patients with high suspicion on MRI (PI-RADS≥4), which could be as high as 64% [21]. Even though PSMA is considered to have superior sensitivity and specificity to mpMRI, it still exhibits a certain rate of false negatives. PSMA imaging showed sensitivity of 92% in detecting PCa, suggesting a false positive rate of 8%. When used in conjunction with mpMRI, the false positive rate is reduced to 2% [22]. Our previous study revealed that patients with a score of 4 on PSMA PET/MRI were reliably diagnosed with PCa using the PSMA PET/MRI-guided ultrasound fusion TB [11]. These findings were consistent with the report by Meissner et al. [23]. In this retrospective study, patients were assessed using mpMRI and PSMA PET, and all patients were confirmed as PCa with positive findings. Therefore, we enrolled these patients in our study to assess the diagnostic value of the TB.

In this study, all selected patients were diagnosed with PCa based on the pathological results. We still chose the miPSMA score as the diagnostic criterion, recognizing that different centers may employ varying maximum standardized uptake values (SUV_{max}) due to the use of different radiotracers. Additionally, the choice of different SUV_{max} as diagnostic thresholds may influence diagnostic efficacy. Utilizing a SUV_{max} threshold of 8 for diagnosis, the accuracy rates for PCa were found to be 87.7%, 89.3%, and 100% for tumors with the GS of 1, GS of 2, and GS of ≥3, respectively [24]. However, some lesions initially missed by SB lesions were subsequently confirmed to be cancerous with the repeated biopsy. While no significant disparity was observed in the detection of PCa between the two groups,

Table 4 Clinical and histopathologic characteristics of patients with repeat biopsies in the systematic biopsy group.

Case	Age, year	BMI, kg/m^2	tPSA, ng/mL	fPSA, ng/mL	f/t PSA	PV, mL	PSAD, ng/mL^2	GS of the repeat biopsy	GS of the postoperative specimen	Lesion's location	Core (positive core), n	PSM	PLND	Positive lymph node
1	69	24.2	10.37	2.67	0.26	25.2	0.41	4+4	4+3	Right apex	3 (2)	No	No	/
2	80	25.0	19.35	1.61	0.08	38.4	0.50	4+4	4+5	Anterior	3 (3)	No	No	/
3	64	28.4	19.14	1.38	0.07	49.3	0.39	3+5	4+5	Anterior	3 (3)	Yes	No	/
4	80	26.1	29.52	2.36	0.08	59.0	0.50	4+5	4+4	Anterior and apex	3 (3)	Yes	Yes	No
5	64	24.4	12.73	1.00	0.08	27.1	0.47	3+4	4+3	Anterior	3 (3)	Yes	No	/

BMI, body mass index; PSA, prostate-specific antigen; tPSA, total PSA; fPSA, free PSA; f/tPSA, the ratio of fPSA to tPSA; PV, prostate volume; PSAD, PSA density; GS, Gleason score; PSM, positive surgical margin; PLND, pelvic lymph node dissection; /, without PLND.

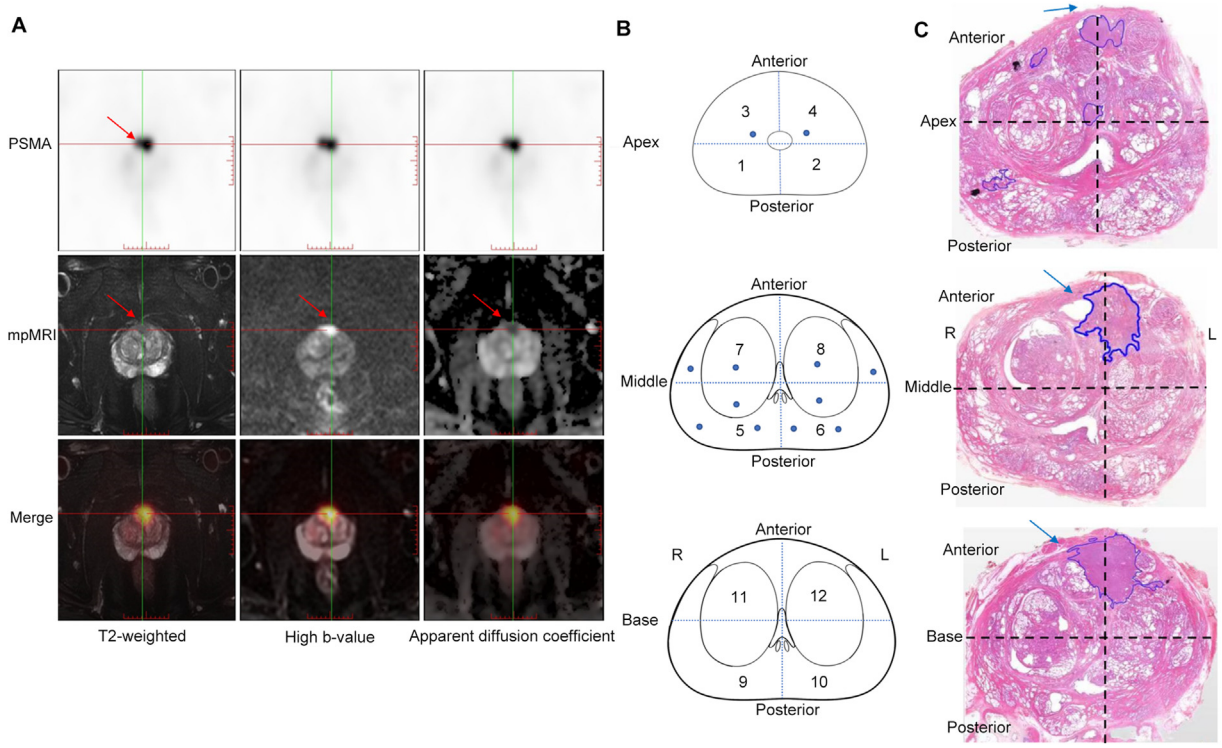

Figure 2 Results for a 66-year-old man with a prostate-specific antigen level of 7 ng/mL whose previous 12-core systematic biopsy was negative. (A) The results of ^{18}F-DCFPyL PET/MRI (the red arrow showing a high focal PSMA ligand uptake in the anterior region of prostate, highly suspicious for PCa with a score of 3 according to the standardized PCa molecular imaging evaluation criteria; the T2-weighted image showing a moderate hypointense area with corresponding diffusion restriction in both high b-value and apparent diffusion coefficient images in the same position (red arrow) with a PI-RADS of 4; the merge means the fusion image of PSMA and mpMRI); (B) The schematic diagram of the 12-segment division map of the prostate (four segments for each level at the apex, middle, and base of prostate, marked by 12 numbers) and the systematic biopsy (the blue point); (C) Hematoxylin and eosin gross section histopathology showing a corresponding International Society of Urological Pathology Grade 3 tumor focus (outlined by the blue circle and blue arrow; 12-segment division). PCa, prostate cancer; PSMA, prostate-specific membrane antigen; mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging Reporting and Data System; R, right; L, left.

the rate of detecting csPCa was notably higher in the PSMA PET/MRI-guided TB group compared with the SB group. A comparison of the biopsy results and operative specimens in our study revealed that the PSMA PET/MRI-guided fusion TB had a lower upgrade rate than the SB. Pathological upgrading is a prevalent concern in clinical settings, with incidence rates ranging from 30% to 45% following the SB [25]. An inaccurate pathological result may lead to flawed risk stratification, potentially prompting unsuitable treatment strategies [26]. Such strategies may lead to the PSM or PSA level persistence after RP. The PSM and persistent PSA level were associated with an elevated risk of recurrence and poorer prognoses. A PSA level of $>$0.1 ng/mL at 4—8 weeks postoperatively was commonly used as the cut-off value to indicate persistent local disease [27,28]. Thus, we recorded instances of the PSM and PSA level of $>$0.1 ng/mL at the 6-week follow-up visit. No statistically significant differences were found between the groups in terms of the PSM and PSA level at 6 weeks postoperatively. Consequently, it suggests that the TB alone in these patients may not lead to a inappropriate surgical strategy and unfavorable prognosis.

No significant differences were observed between the groups in terms of complications, such as pain, anxiety, bleeding, or hematuresis. According to a study by Tops et al. [7], reducing the number of biopsy cores was found to be associated with lower risk of infectious complications. This could be attribute to the use of a transperineal biopsy approach [29]. Moreover, whether these results are associated with our limited sample size requires further research.

In comparison to TB, up to 79% of the csPCa lesions located in the anterior stromal regions are frequently missed by the SB [30]. In the control group in this study, five patients initially received a negative biopsy result, but were subsequently diagnosed with PCa through the TB. Four of these missing cancerous lesions were located in the anterior stromal regions which are commonly missing by the SB due to the block of pubic symphysis.

Prior to surgery for confirmed cases, PSMA PET is recommended as a tool for preoperative screening of metastasis and its ability to diagnose and stage PCa was proved. In this study, we included patients with a PI-RADS score of $\geq$4, where the probability of tumor diagnosis was exceptionally high. Given that PSMA PET has a NPV of up to 88% for the diagnosis of PCa, if the PSMA PET examination is conducted prior to the biopsy, we can potentially reduce the number of biopsy needles for positive patients [31]. For

patients with negative results, it is hoped that the biopsy results can be used to exclude false positive MRI findings. Of course, the negative scenario for PSMA is speculative and requires further research and discussion.

The strengths of our study are as follows. This is a prospective RCT that collected the comprehensive histological data for both biopsies and operative specimens. In a single-center RCT involving 120 men, the PSMA PET/CT-guided TB detected significantly more cases of PCa and csPCa than the transrectal ultrasonography-guided biopsy [32]. In another study, the PSMA PET/MRI-guided biopsy was found to be promising for PCa diagnosis, with a reduction in the number of unnecessary prostate biopsies [33]. The PSMA PET/MRI-guided TB for csPCa showed patient-based sensitivity, specificity, NPV, positive predictive value, and accuracy of 96%, 81%, 93%, 89%, and 90%, respectively [8]. Although these studies demonstrated PSMA PET/MRI to be a promising alternative for PCa detection, they lack a direct comparison between biopsies and operative specimens, which our study aimed to address.

The main limitation of our study was the selection of the study population. We confined our analysis to selected patients, but in clinical practice, there would be more patients with negative or equivocal imaging results. Whether these populations could benefit from pre-biopsy PSMA PET/MRI examination remains unclear. Additionally, our sample size is small. Moreover, our follow-up period was not sufficient to show long-term outcomes of the procedure, which are yet to be identified. Lastly, we only performed comparisons between the 3-core TB and standard biopsy strategy. It is generally recommended to combine the TB with the SB. Considering if the PSMA PET/MRI-guided TB and SB were performed in the same patient, the result of one method may be influenced by the other. Therefore, these limited the comparison between the TB and SB groups. Future studies should explore the comparison between the TB and combined biopsy to provide a more comprehensive understanding.

5. Conclusion

Our findings suggest that selected patients who have undergone a pre-biopsy PSMA PET/MRI examination and scored 4, may benefit from the subsequent TB, with no impact on their post-surgery prognosis.

Author contributions

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Drafting of manuscript: Liyan Ao.
Critical revision of the manuscript: Shaoxi Niu, Xu Zhang.

Conflicts of interest

The authors declare no conflict of interest.

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