ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2021 December 26; 9(36): 11122-11508

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
December 26, 2021

INSTRUCTIONS TO AUTHORS
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https://www.wjgnet.com/bpg/GerInfo/288

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https://www.wjgnet.com/bpg/gerinfo/242

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World J Clin Cases 2021 December 26; 9(36): 11183-11192

DOI: 10.12998/wjcc.v9.i36.11183

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Cognitive magnetic resonance imaging-ultrasound fusion transperineal targeted biopsy combined with randomized biopsy in detection of prostate cancer

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Institutional review board statement: This study was reviewed and approved by the Institutional Review Board of

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Abstract

BACKGROUND

Prostate cancer (PCa) is one of the most common cancers among men. Various strategies for targeted biopsy based on multiparametric magnetic resonance imaging (mp-MRI) have emerged, which may improve the accuracy of detecting clinically significant PCa in recent years.

AIM

To investigate the diagnostic efficiency of a template for cognitive MRI-ultrasound fusion transperineal targeted plus randomized biopsy in detecting PCa.

Beijing Hospital (2018BJYYEC-028-02).

Informed consent statement: Written informed consent was obtained from the patient or his/her guardians prior to the study.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Supported by the Beijing Hospital Clinical Research 121 Project (BJ-2018-090 to Ming Liu).

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 20, 2021
Peer-review started: January 20, 2021
First decision: September 28, 2021
Revised: October 15, 2021
Accepted: November 3, 2021

METHODS

Data from patients with an increasing prostate-specific antigen (PSA) level but less than 20 ng/mL and at least one lesion suspicious for PCa on MRI from December 2015 to June 2018 were retrospectively analyzed. All patients underwent cognitive fusion transperineal template-guided targeted biopsy followed by randomized biopsy outside the targeted area. A total of 127 patients with complete data were included in the final analysis. A multivariable logistic regression analysis was conducted, and a two-sided $P < 0.05$ was considered statistically significant.

RESULTS

PCa was detected in 66 of 127 patients, and 56 cases presented clinically significant PCa. Cognitive fusion targeted biopsy alone detected 59/127 cases of PCa, specifically 52/59 cases with clinically significant PCa and 7/59 cases with clinically insignificant PCa. A randomized biopsy detected seven cases of PCa negative on targeted biopsy, and four cases had clinically significant PCa. PSA density (OR: 1.008, 95%CI: 1.003-1.012, $P = 0.001$; OR: 1.006, 95%CI: 1.002-1.010, $P = 0.004$) and Prostate Imaging-Reporting and Data System (PI-RADS) scores (both $P < 0.001$) were independently associated with the results of cognitive fusion targeted biopsy combined with randomized biopsy and targeted biopsy alone.

CONCLUSION

This single-centered study proposed a feasible template for cognitive MRI-ultrasound fusion transperineal targeted plus randomized biopsy. Patients with higher PSAD and PI-RADS scores were more likely to be diagnosed with PCa.

Key Words: Prostate neoplasms; Magnetic resonance imaging; Cognitive fusion; Prostate biopsy; Prostate cancer

Core Tip: Prostate biopsy remains the standard diagnostic modality before curative treatment. Cognitive magnetic resonance imaging (MRI)-ultrasound fusion biopsy is a more accessible and economical biopsy technique for small-sample institutions to realize imaging-guided targeted biopsy. In this study, we proposed a customized template and reported a feasible approach for cognitive MRI-ultrasound fusion biopsy with our single institutional experience. The results from this retrospective study revealed that a high yield of cancer, and that patients with higher prostate-specific antigen density and Prostate Imaging-Reporting and Data System scores are more likely to be diagnosed with prostate cancer under this biopsy strategy.

Citation: Pang C, Wang M, Hou HM, Liu JY, Zhang ZP, Wang X, Zhang YQ, Li CM, Zhang W, Wang JY, Liu M. Cognitive magnetic resonance imaging-ultrasound fusion transperineal targeted biopsy combined with randomized biopsy in detection of prostate cancer. *World J Clin Cases* 2021; 9(36): 11183-11192
URL: https://www.wjgnet.com/2307-8960/full/v9/i36/11183.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i36.11183

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancers and the second leading cause of cancer-related deaths among men in the United States[1]. Prostate biopsy remains the standard modality for PCa diagnosis. Traditionally, a biopsy is primarily conducted under transrectal and systematic ultrasound guidance[2]. However, the detection rate of the initial biopsy is unsatisfactory, with an overall yield of only 22%-29% reported in previous studies[3,4] due to sampling error or technical limitations resulting from the location of the tumor (*i.e.*, anterior tumor, which accounts for approximately 21% of all PCa). Moreover, a higher risk of detecting lower-grade cancer while missing clinically significant PCa (csPCa) occurs by traditional systematic

Article in press: November 3, 2021
Published online: December 26, 2021

P-Reviewer: Leowattana W
S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

biopsy (SBx), which may increase the probability of overtreatment or underestimation of PCa burden and aggressiveness.

Targeted biopsy (TBx) based on multiparametric magnetic resonance imaging (mp-MRI), which has emerged as a potential method for the detection, localization, stratification, and staging of PCa, is promising in overcoming the above challenges of traditional SBx[5-8].Various strategies of TBx have been reported in previous studies, with the software registration mp-MRI-ultrasound fusion TBx and mp-MRI in-bore TBx studied most. Cognitive MRI-ultrasound fusion TBx (COG-TB) is a more economical and accessible targeted biopsy strategy, especially for small institutions or those without fusion software or equipment for MRI in-bore biopsy; however, primarily based on the operator's tumor identification, COG-TB requires a higher level of experience and more easily followed template to reduce operator variability, and there are sparse data on the optimal template and predictors for the detection rate of COG-TB. Moreover, patients with high prostate-specific antigen (PSA) levels (*i.e.*, PSA > 20 ng/mL) were included in previous studies on the influencing factors of the detection rate, which may cause selection bias and result in a detection rate.

Thus, this retrospective study was conducted to propose a feasible template for COG-TB with our single institutional experience on a biopsy-naïve cohort with a PSA level that was elevated but < 20 ng/mL to evaluate the detection rate for csPCa of COG-TB followed by randomized biopsy (SBx) and to investigate potential influencing factors.

MATERIALS AND METHODS

Study population

We retrospectively studied a total of 127 biopsy-naïve men from December 2015 to June 2018, with increasing PSA levels < 20 ng/mL and detectable lesions suspicious for PCa on mp-MRI undergoing transperineal template-guided COG-TB followed by SBx outside the targeted area. The study was approved by the Institutional Review Board of Beijing Hospital (2018BJYYEC-028-02).

MRI protocols

All patients underwent pelvic MRI approximately 1 wk before the biopsy. All mp-MRI examinations were performed using a 3.0 T scanner (c 3T; GE, Discovery 750, America), including multiplanar turbo spin-echo T2-weighted imaging (T2WI, TR/TE = 4800/90 ms, slice thickness: 4 mm, interslice gap: 1 mm, FOV = 28 cm, matrix = 334 × 336) and axial diffusion-weighted imaging (DWI, TR/TE = 4000/80 ms, slice thickness: 4 mm, interslice gap: 1 mm, FOV = 22 cm, NEX = 3, matrix = 128 × 128, B values of 0, 1000, 1400, and 2000 s/mm^2).

MRI interpretation

Two experienced (at least 3 years) radiologists who were blinded to the biopsy results evaluated the mp-MRI data separately and independently located each suspicious lesion based on the Prostate Imaging-Reporting and Data System version 2.1 (PI-RADS v2.1)[9,10]. Additionally, the maximum dimensions of the suspicious lesion were measured on axial T2WI, and the prostate volume was calculated by multiplying the dimensions of the prostate gland in all three different planes × 0.52. The two radiologists independently reviewed all data to achieve consensus.

Biopsy strategies

First, general anesthesia was administered, then positioned the patient in a lithotomy with the scrotum elevated anteriorly using microporous tape to expose the perineum. Next, the biplanar TRUS probe was fixed on a stepper stabilizer device, such that the TRUS probe could be propelled forward and backward by a specific distance to localize the targeted layer to be consistent with images on mp-MRI. A grid was then placed on the stepper stabilizer device ahead of the perineum to guide the biopsy gun. The urethra was visible on TRUS images using an indwelling Foley catheter (Figure 1).

The urologist reviewed the MRI and the report before the biopsy. MRI transverse images were obtained every 5 mm, and the layer intervals on the TRUS images were set to 5 mm using the stepper stabilizer device. The first step of cognition was to identify the apex and base of the prostate and then determine the corresponding layer containing the targeted lesion. The second step was to target the lesion on TRUS images using the urethra, the outline of the prostate, and the boundary between the

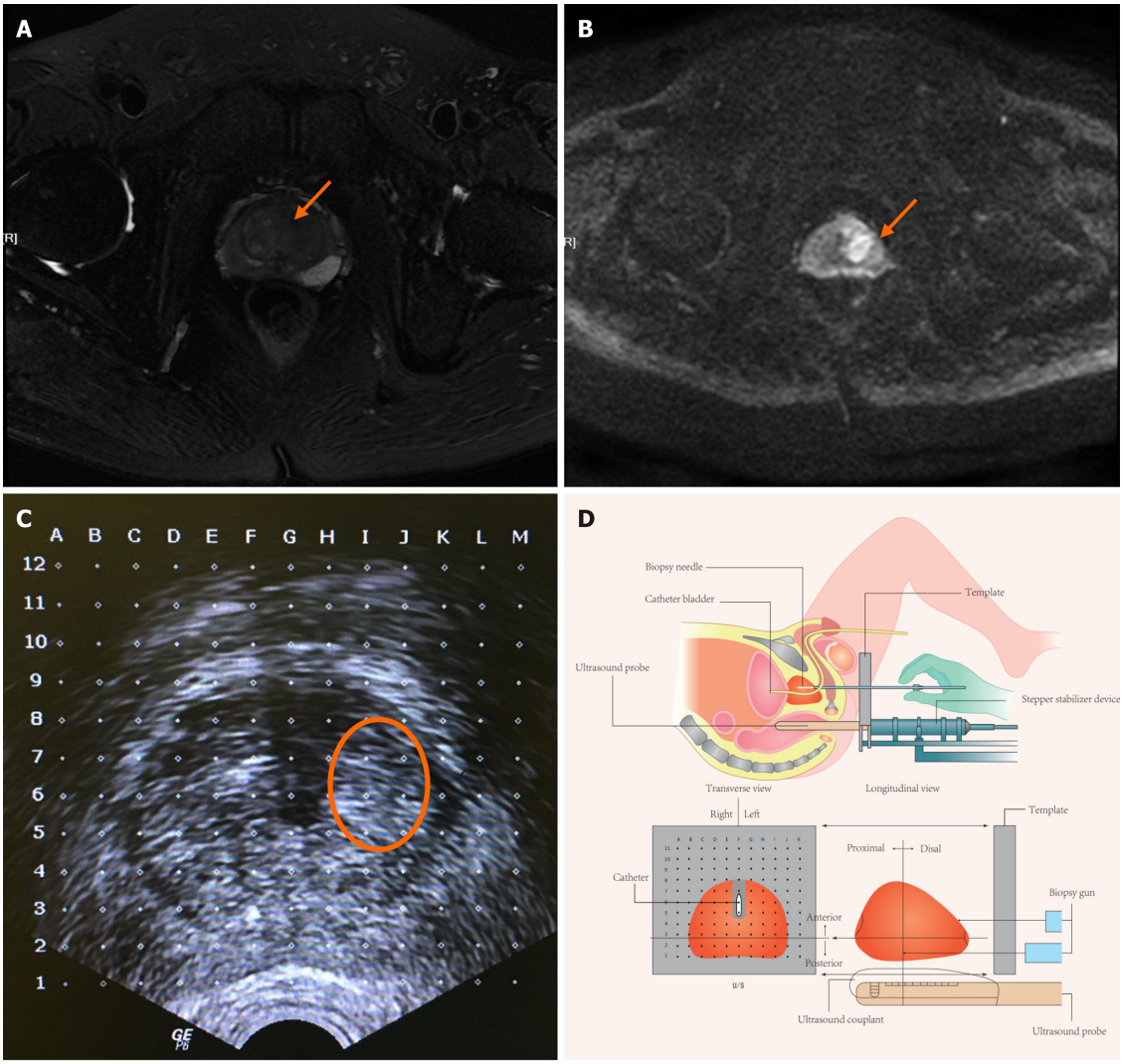

Figure 1 A schema for the transperineal template-guided cognitive magnetic resonance imaging-ultrasound fusion TBx plus randomized biopsy strategy. A: Axial T2-weighted imaging (T2WI); B: Axial diffusion-weighted imaging (DWI) (orange arrow); C: The same plane on transrectal ultrasound imaging with magnetic resonance imaging (MRI); D: The procedure for biopsy. A lesion suspicious for prostate cancer was found with low signal on T2WI and high signal on DWI. The area within the red ellipse was considered the corresponding lesion with MRI identified by cognition and would be recognized as the targeted lesion for biopsy.

peripheral and transitional zones. The targeted biopsy was administered first, with approximately two to four cores obtained per targeted lesion. Transperineal SBx outside the targeted areas was subsequently performed using a custom nine-region template, in which the prostate gland was divided into eight regions in a single plane with the apex of the prostate as an additional ninth region. Generally, two to four cores were obtained within each region according to the prostate gland volume.

Biopsy specimens were collected in formalin and sent for pathological analysis. Finally, grades were determined for each core by a uropathologist based on the International Society of Urological Pathology (ISUP) grading system[11].

Definitions

Suspicious lesions on mp-MRI were defined as lesions with an overall PI-RADS score of 3-5, which could be considered candidate lesions for targeted biopsy.

csPCa was defined as a PCa lesion with a Gleason score ≥ 7 (ISUP ≥ 2), maximum cancer core length ≥ 4 mm, or both[12].

Statistical analysis

The age, BMI, prostate volume, PSA, PSA density for each patient, tumor dimension, location, and PI-RADS score for each lesion were recorded. Student's **t**-test and Mann-Whitney U test were used for continuous variables. The chi-squared test was used for categorical variables, and a two-sided $P < 0.05$, was considered statistically significant.

Univariate and multivariate logistic regression analyses were then conducted to screen for the influencing factors. All analyses were performed using SPSS statistical software (Version 24, IBM, Armonk, NY, United States).

RESULTS

Basic information

The basic characteristics of patients, dichotomized by biopsy results are shown in Table 1. The median age was 68 (IQR: 63-74) years with a median PSA level of 8.51 (IQR: 5.43-11.40) ng/mL and a median tumor dimension of 1.10 (IQR: 0.70-1.30) cm. The overall operation time was 30 (20-45) min. After the biopsy, most patients had mild self-limited hematuria and perineal ecchymoses for < 7 days. Only one patient was treated with seminal vesiculoscopy for hemospermia. All procedures were well tolerated without high-grade complications or adverse events (defined as Clavien II or greater)[13] in the remaining cohort of patients.

Cancer detection

PCa was detected in 66 of the 127 patients (51.9%), of which 56 (44.1%) were csPCa. Urothelial carcinoma was detected in one case and was found to be positive only for COG-TB, which was not included in further analysis stratified by csPCa status. COG-TB alone detected 59/127 cases with PCa (46.5%), specifically 52/59 cases with csPCa (88.1%) and 7/59 cases with clinically insignificant PCa (11.9 %). Transperineal SBx detected 7 cases of PCa negative on COG-TB, of which 4 were csPCa, suggesting an approximate 7.1% added value to the result of COG-TB alone.

No significant differences in BMI, PSA level, tumor location, or total biopsy cores (all $P > 0.05$), whereas differences were found in age, prostate volume, PSA density (PSAD), maximum dimension, and PI-RADS scores were noted between patients with positive and negative results (all $P < 0.05$) (Table 1). Regarding csPCa status, age, prostate volume, PSAD, tumor dimension, and PI-RADS score also differed significantly (all $P < 0.05$) between patients with or without a diagnosis of csPCa (Table 2).

Influence factors for biopsy results

The results of logistic regression analysis showed that PSAD (OR, 1.008; 95%CI: 1.003-1.012, $P = 0.001$) and PI-RADS score ($P < 0.001$) were independent risk factors for COG-TB with SBx (Table 3). For COG-TB alone, PSAD (OR: 1.006, 95%CI: 1.002-1.010, $P = 0.004$) and PI-RADS score ($P < 0.001$) again appeared independently associated with biopsy result. Although tumor location did not independently influence the biopsy result, tumors involving TZ and PZ were more likely to be positive for COG-TB alone than tumors within the TZ (OR: 10.429, CI 95%: 1.218-89.285, $P = 0.032$) (Table 3).

DISCUSSION

TRUS-guided biopsy (TRUS-Bx) has long been the standard of care for prostate biopsy and still represents the reference standard modality for diagnosing PCa[2]. However, multiple studies have demonstrated that TRUS-Bx may lead to the absence of csPCa while detecting more insignificant PCa than the new strategy of MRI-guided TBx[14], and the transrectal approach may result in more infection-related complications than the transperineal approach[15,16]. Thus, image-guided biopsy *via* a transperineal approach has become promising and has been the focus of research in recent years.

One of the attractive features of TBx is its high detection rate. Earlier studies mostly focused on comparing TBx with TRUS-Bx in patients with at least one previous negative result[17-23], and the overall PCa detection rate is the most commonly used primary endpoint. Hadashick[24] and Miyagawa *et al*[25] reported two series of studies comparing transperineal TBx and transperineal TRUS-Bx performed on the same patient simultaneously. Overall PCa detection rates of 59% and 61% have been reported, respectively. However, the detection rate of csPCa was unknown in either study. Veeru *et al*[26] reported a detection rate of 57% (103/182) using transperineal TBx. The overall detection rates of PCa and csPCa for COG-TB alone in this study were 46.5% and 40.9%, respectively. Regarding the combination of COG-TB and SBx, the detection rates increased to 52.8% and 44.1%, respectively. The possible reasons for the lower detection rate in our study may be as follows: First, the inclusion criteria were

Table 1 Patients' characteristics dichotomized by negative and positive biopsy results

	Total cohort	Negative biopsy	Positive biopsy	*P* value
Patients, *n*	127	60	67	-
Age (yr), median (IQR)	68 (63-74)	66 (61-70)	70 (65-78)	< 0.001
BMI (kg/m^2), median (IQR)	24.8 (22.64-26.54)	24.48 (23.03-26.56)	24.77 (22.49-26.26)	0.466
PSA (ng/ml), median (IQR)	8.51 (5.43-11.40)	7.04 (5.06-11.01)	8.96 (5.81-12.01)	0.056
Prostate volume (cm^3), median (IQR)	36.30 (26.80-46.20)	42.67 (31.58-58.23)	32.10 (23.20-39.65)	< 0.001
PSAD (ng/ml/cm^3), median (IQR)	0.23 (0.14-0.34)	0.16 (0.12-0.25)	0.30 (0.18-0.43)	< 0.001
Largest dimention (cm), median (IQR)	1.10 (0.70-1.30)	1.05 (0.53-1.28)	1.10 (0.80-1.40)	
PI-RADS	4 (3-5)	3 (3-5)	4(3-5)	< 0.001
3 (*n*/%)	57 (44.9)	46 (76.7)	11 (16.4)	
4 (*n*/%)	41 (32.3)	12 (20.0)	29 (43.3)	
5 (*n*/%)	29 (22.8)	2 (3.3)	27 (40.3)	
Location, *n* (%)				0.054
TZ	41 (32.3)	23 (38.3)	18 (26.9)	
PZ	75 (59.1)	35 (58.3)	49 (59.7)	
Both	0.054	2 (3.3)	9 (13.4)	
Total cores, *n*, median (IQR)	19 (17-22)	20 (18-22)	18 (15-22)	0.046
Targeted	5 (4-8)	5 (3-8)	6 (4-8)	
Randomized	14 (11-16)	14 (12-16)	13 (10-16)	

PSA: Prostate-specific antigen; PSAD: PSA density; PI-RADS: Prostate Imaging Reporting and Data System; TZ: Transitional zone; PZ: Peripheral zone.

Table 2 Patients' characteristics dichotomized by clinically significant prostate cancer status

	Non-csPca	csPCa	*P* value
Patients, *n*	71	56	-
Age (yr), median (IQR)	66 (62-70)	70 (65-78)	0.001
BMI (kg/m^2), median (IQR)	24.50 (23.05-26.70)	24..75 (22.48-25.95)	0.144
PSA (ng/mL), median (IQR)	7.32 (5.16-11.69)	8.88 (5.76-11.14)	0.277
Proatate Volume (mL), median (IQR)	41.02 (30.90-53.50)	31.95 (23.39-39.65)	0.001
PSAD (ng/mL/cm^3), median (IQR)	0.18 (0.13-0.26)	0.30 (0.21-0.40)	0.003
Largest dimention (cm), median(IQR)	1.00 (0.60-1.30)	1.10 (0.83-1.48)	0.04
PI-RADS	3 (3-5)	4 (3-5)	0.001
3, *n* (%)	47 (66.20)	10 (17.86)	
4, *n* (%)	19 (26.76)	22 (39.29)	
5, *n* (%)	5 (7.04)	24 (42.86)	
Total cores, *n* (IQR)	19 (17-22)	18 (15-21)	0.097

Non-csPCa: Clinically insignificant prostate cancer; csPCa: Clinically significant prostate cancer; PSA: Prostate-specific antigen; PSAD: PSA density; PI-RADS: Prostate Imaging Reporting and Data System; TZ: Transitional zone; PZ: Peripheral zone.

more rigorous given the requirements of PSA level < 20 ng/mL and biopsy naïve history. Second, the differences in the strategy of targeted biopsy and thresholds for declaring a suspicious lesion on mp-MRI may also contribute to the difference in detection rates.

Table 3 Multivariate logistic regression analysis of biopsy results of cognitive fusion targeted biopsy with/without randomized biopsy

	With randomized biopsy			Without randomized biopsy		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age	1.052	0.977-1.133	0.177	1.018	0.945-1.097	0.640
PSAD	1.008	1.003-1.012	0.001	1.006	1.002-1.010	0.004
PI-RADS score			< 0.001			< 0.001
3	Ref.	Ref.		Ref.	Ref.	
4	8.167	2.599-25.662	< 0.001	4.394	1.431-13.491	0.010
5	35.474	5.655-222.507	< 0.001	54.266	8.141-361.724	< 0.001
Tumor dimension	1.060	0.304-3.690	0.928	0.960	0.281-3.277	0.948
Tomor location			0.198			0.063
TZ	Ref.	Ref.		Ref.	Ref.	
PZ	2.086	0.673-6.464	0.203	2.904	0.875-9.637	0.081
Both	6.144	0.687-54.935	0.104	10.429	1.218-89.285	0.032
Total cores	0.981	0.857-1.124	0.786			

PSAD: PSA density; PI-RADS: Prostate Imaging Reporting and Data System; TZ: Transitional zone; PZ: Peripheral zone.

Another promising feature of TBx is its potential to reduce unnecessary cores taken without compromising the detection rate of csPCa. Recently, several prospective multicenter studies have proved the superiority of TBx over TRUS-Bx in the detection of csPCa. The PROMIS study[27] assessed mp-MRI and SBx against template prostate mapping biopsy in biopsy-naïve men and showed that mp-MRI was significantly more sensitive than SBx in detecting cancer ISUP grade group 3 or higher tumors or tumors with cancer core lengths > 6 mm. Another multicenter study (PRICISION)[28] assigned biopsy-naïve men to either TBx or SBx, and the results showed a significantly higher detection rate in the TBx group. Owing to the superiority of TBx in detecting csPCa, several studies have concluded that additional SBx can be omitted[29]. However, it remains controversial whether SBx should be abandoned when performing TBx[30,31]. A recently published prospective study (MRI-FIRST)[32] found no differences between SBx and TBx in the detection rate of ISUP grade group 2 or higher PCa, but the combination of these techniques showed added value, concluding that systematic biopsy cannot be avoided. In the current study, we applied a combined approach with COG-TB followed by SBx. The results showed that COG-TB alone missed 4/56 csPCa, and SBx provided an added value of approximately 7.4%, which should not be neglected. A total of 4.5 (1-12) and 14 (3-33) cores were taken for the targeted and SBx regions, respectively. This variation is mainly due to differences in prostate volume and the number of targeted regions. Furthermore, we applied a customized model that is easier to follow than those reported in previous studies[33], wherein the gland was cut into eight regions in a single plane with the apex of the prostate as the extra ninth region. After TBx, two-four cores were collected within each region outside the targeted lesions. We proposed this model to further standardize the biopsy scheme and reduce the maximum number of cores taken while guaranteeing a systematic sampling method. In this study, a feasible and safe follow-up method was developed.

Tumor dimension, PI-RADS score, prostate volume, and PSAD may influence the detection rate[34]. The results of our study are consistent with previous results, and we conducted further analysis on predictors of TBx. Lesions with a higher PSAD and PI-RADS score may be more likely to be positive for COG-TB. Moreover, lesions involving both the PZ and TZ were more likely to be positive for COG-TB, probably due to the larger tumor size. However, the cores taken from per-targeted lesions were not independent risk factors. A sufficient number of cores taken for the targeted region represents a possible reason for this result[28].

This study has some limitations. First, this was a single-centered retrospective analysis, the conclusions of which needs to be further confirmed by prospective multicentered studies. Second, all men included in the study were preselected using mp-MRI, which probably resulted in a higher positive result. Finally, various

definitions of csPCa were employed in previous studies, whereas we only applied one definition in our study, the results of which will definitely be heterogeneous with studies using different definitions. Despite these limitations, the current study proposed a novel template for prostate SBx after TBx and a feasible approach for COG-TB combined with SBx with a relatively high detection rate. Several potential influencing factors were found that could serve as a reference for the stratification of biopsy patients.

CONCLUSION

The current study proposed a feasible approach for COG-TB combined with randomized biopsy using a cognitive fusion technique with an encouraging detection rate of csPCa and decreasing risk of missing lesions negative on mp-MRI. Patients with higher PSAD and PI-RADS scores were more likely to be positive under this biopsy strategy.

ARTICLE HIGHLIGHTS

Research background

Various strategies for targeted biopsy (TBx) based on multiparametric magnetic resonance imaging (mp-MRI) have emerged, which may improve the accuracy of detecting clinically significant PCa in recent years. Cognitive fusion targeted biopsy is a more ecnomical and accessible strategy but requires more experience.

Research motivation

As cognitive fusion targeted biopsy requires higher level of experience, a more easily followed template would be meaningful for the generalization of this technique and could help reduce operator variability.

Research objectives

To investigate the diagnostic efficiency of a template for cognitive MRI-ultrasound fusion transperineal targeted plus randomized biopsy in detecting PCa, and to evaluate the potential influencing factors for the detection rate.

Research methods

Patients with elevated PSA levels but less than 20 ng/mL, and having at least on suspicious lesion on MRI were retrospectively studied. The detection rate of all cancer and clinically significant cancer were calculated. Multivariate logistic regression analysis was used to analyze the potential influencing factors.

Research results

Cognitive fusion targeted biopsy alone detected 59/127 cases of PCa, specifically 52/59 cases with clinically significant PCa (csPCa) . A randomized biopsy showed an approximate 7.1% added value for csPCa detection. PSA density and PI-RADS score were independently associated with the results of cognitive fusion targeted biopsy combined with randomized biopsy and targeted biopsy alone.

Research conclusions

This single-centered study proposed a feasible template for cognitive MRI-ultrasound fusion transperineal targeted plus randomized biopsy. Patients with higher PSAD and PI-RADS scores were more likely to be diagnosed with PCa using this biopsy strategy.

Research perspectives

Prospective multicentered studies are needed to further test our template and to confirm the influencing factors for the detection rate.

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