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Free-hand transperineal targeted prostate biopsy with real-time fusion imaging of multiparametric magnetic resonance imaging and transrectal ultrasound: single-center experience in China

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Abstract
Objectives To report our experience with free-hand transperineal targeted biopsy with real-time transrectal ultrasound (TRUS) and multiparametric magnetic resonance imaging (mpMRI) fusion images for the diagnosis of prostate cancer (PCa).
Patients and methods A total of 62 consecutive patients suspicious of PCa at the mpMRI scan and PSA >4.0 ng/mL were recruited prospectively. Targeted biopsies (TBs) were carried out for each cancer-suspicious lesion and followed a 12-core systematic biopsy (SB) protocol. Pathological findings of TB and SB were analyzed.
Results The age of the patients was 68.38 ± 6.57 years (range 51–79 years). The preoperative PSA value was 10.21 ± 5.57 ng/mL (range 4.5–30.1 ng/mL). Preoperative prostate volume was 34.05 ± 9.86 mL (range 19–64 mL). The PCa patients detected by SB and/or TB were 34 (54.8 %). Cancer-detected rates of SB and TB cores were 7.53 and 26.2 %, respectively ($P < 0.001$). The positive core length of SB and TB cores was 3.71 ± 2.77 mm (range 1–14 mm) and 5.00 ± 3.04 mm (range 2–17 mm), respectively ($P = 0.016$). The positive core percent of SB and TB cores was 28.77 ± 20.13 % (range 7–100 %) and 35.76 ± 18.73 (range 11–100 %), respectively ($P = 0.048$). Moreover, clinically significant PCa cores detected by the SB and TB were 19 cores (2.6 %) and 48 cores (18.5 %), respectively ($P < 0.001$).
Conclusions Free-hand transperineal TB using real-time TRUS and mpMRI fusion imaging has the ability to improve sampling quality and detect more clinically significant PCa compared with SB.

Keywords Fusion image · Magnetic resonance imaging · Prostate cancer · Targeted biopsy · Transrectal ultrasound

Introduction

Transrectal ultrasonography (TRUS) is a common diagnostic procedure for detecting prostate cancer (PCa). Despite an increasing number of biopsy cores being included in TRUS-guided biopsy protocols, the current standard of including 10–14 randomized cores still lacks sensitivity and often detects clinically insignificant disease [1–3]. Despite limited ability to delineate PCa, TRUS-guided prostate biopsies have the virtues of speed, ease, cost, availability, portability and are more suitable for wide-area sampling of the prostate, including far-lateral peripheral zones [4].

Among the various modalities of prostate imaging, multiparametric magnetic resonance imaging (mpMRI) offers an increased sensitivity and specificity and has become the standard imaging technique for biopsy guidance [5, 6]. The concept of targeted biopsies (TBs) on suspicious areas emerged in the early 2000s in order to improve sensitivity to detect clinically significant PCa through MRI guidance [7]. However, MRI is not widely available for image-guided procedures. Even simple prostate biopsies taken under direct MRI guidance can take hours and require highly specialized MRI-compatible equipment [8].

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To take advantage of both modalities for prostate management, many researchers have explored fusion technologies where MRI data and real-time US images are fused to benefit diagnosis and/or biopsy [9]. The mpMRI–TRUS image fusion biopsy system is a novel fusion imaging technology which can typically or accurately fuse real-time US images with that of computed tomography (CT) or MRI volume data and then displays them on the same monitor side by side. This means that the clinician can visualize both registered multiplanar reconstruction images on the same monitor to make diagnostic/procedural decisions in real time [4].

In this paper, we provide our single-center early experience of using mpMRI–TRUS image fusion technology for prostate biopsy and comparing prostate biopsy performance for free-hand transperineal TB guided by mpMRI–TRUS with that of 12-core systematic biopsy (SB) in the detection of PCa in China.

Patients and methods

Study population

From August 2014 to November 2014, after receiving institutional review board approval, patients with PSA level greater than 4.0 ng/mL underwent mpMRI prospectively. All these patients were assessed with prostate mpMRI in the radiology department of our hospital and were considered having at least one suspicious area in mpMRI images. No patients had any previous history of prostate biopsy. All patients had given informed consent.

Multiparametric MRI Examination and Analysis

Multiparametric prostate MRI was performed with a 3.0-T MR scanner (Achieva 3.0T TX dual-source parallel RF excitation and transmission technology, Philips Medical Systems, The Netherlands) by using a 32-channel phased array coil. Transverse/coronal/sagittal (18 slices, thickness 3 mm/gap 0.5 mm, TR 3744 ms, TE 120 ms, number of signals acquired 2, resolution 1.49 mm × 1.51 mm) T_2-weighted turbo spin-echo (TSE) images were acquired. Diffusion-weighted imaging, spin-echo–echo-planar images (18 slices, thickness 6 mm, intersection gap 1 mm, TR 925/TE 41 ms, number of signals acquired 1, resolution 3 mm × 3 mm, b-factor 0/800 s/mm^2) were acquired. And T_1 high-resolution isotropic volume with fat suppression after gadolinium injection was employed for dynamic contrast-enhanced images (133 slices, thickness 3 mm, no intersection gap, TR 3.1/TE 1.46 ms, number of signals acquired 1, resolution 1.49 mm × 1.51 mm, dynamic scan time 00:06.9). Mappings of the apparent diffusion coefficient (ADC) were generated from b 0 and b 1000 images of DWI using the Philips WorkStation software (Extended Workspace, EWS).

All MRI scans were reviewed by an experienced radiologist (B.Z.) with no prior clinical information. Suspicious areas, so-called region of interest (ROI), were defined, and the radiologist provided a likelihood score that clinically significant cancer would be present for each ROI from 2 to 5 on the PI-RAD classification [10] based on a Likert scale according to the European Society of Urogenital Radiology prostate MR guidelines 2012 [11]: 1, most probably benign; 2, probably benign; 3, indeterminate; 4, probably malignant; and 5, highly suspicious of malignancy [10].

mpMRI and TRUS image fusion

All biopsies were conducted with an mpMRI–TRUS biopsy system (RVS®, Real-time Virtual Sonography, Hitachi Medical Corporation, Tokyo, Japan) that provides real-time fusion of TRUS images and MR images to guide the biopsy needles using a transperineal approach. The procedure of MRI fused to the real-time TRUS was as described previously [4, 12]. In brief, the documented lesions were marked first as ROI on morphological, high-resolution transversal T_2W TSE sequences, which were loaded into the biopsy system before. The magnetic field generator was placed near the patients' body, and the magnetic position sensor was mounted on the ultrasound probe to be used for acquiring the TRUS images. The internal urethral orifice was used as the fiducial landmark for registering the MRI and ultrasound images. The MR images reconstructed from the MRI volume data that corresponded to the US sagittal images were displayed adjacent to the US sagittal image on the same monitor. Morphological MRI data including the apparent ROIs were superimposed on the TRUS images in real time to guide the biopsy needle. The system documented the positions of the acquired cores in the Digital Imaging and Communication in Medicine (DICOM) data set of the morphological MRI with consecutive numbers.

Biopsy protocol

The biopsy started with TB to the center of cancer-suspicious lesions without the guide of template using the free-hand transperineal technique (Fig. 1), and then, standard 12-core SB (blinded to the MRI target lesions) was carried out in all patients. Lesions suspicious of cancer identified on MRI were semiautomatically displayed on the real-time TRUS image [13]. All target lesions were sampled once in both axial and sagittal planes, with at least two core biopsies per target. An 18-G automatic biopsy gun with a specimen size of 22 mm (Bard Magnum; Bard Medical, Covington, GA, USA) was used to take biopsy cores. All patients underwent general anesthesia using a larynx mask during the biopsy procedure.

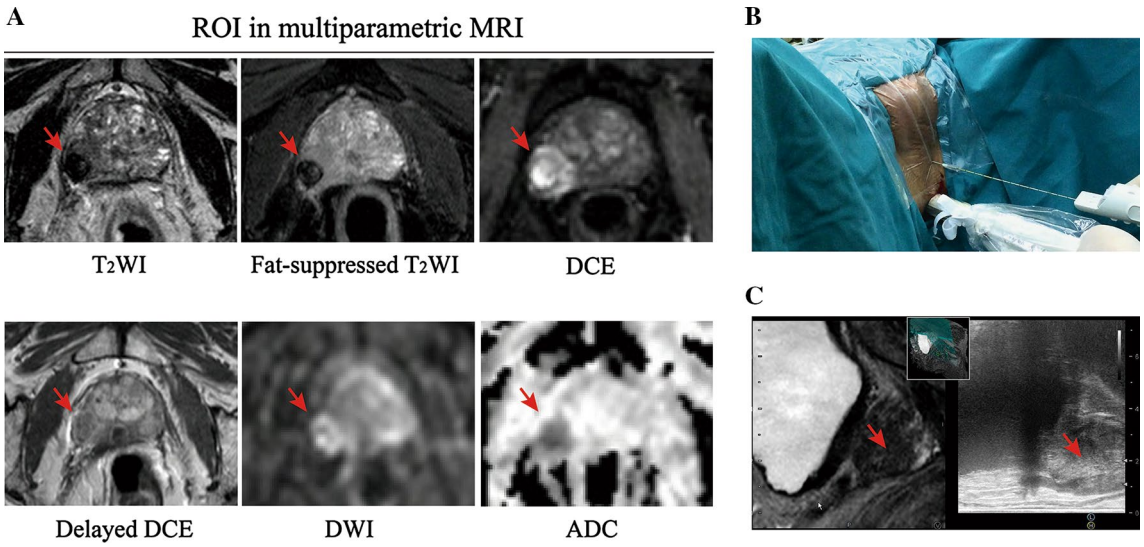

Fig. 1 ROI in prebiopsy mpMRI and the procedure of the free-hand targeted prostate biopsy with real-time fusion imaging of TRUS and mpMRI. This lesion (*arrow*) was detected by prebiopsy mpMRI examination (**a**) and was scored as "highly suspicious" (score 5 of 5). The operator free hand transperineally inserted the needle guided by real-time fusion imaging of TRUS and mpMRI and could obtain the prostate specimens by viewing the sagittal T_2W image of the prostate (**b**, **c**). The mpMRI–US fusion-guided biopsy of the prostate revealed Gleason 4 + 4 tumor in the lesion (95 % core involvement)

Pathological analysis

All biopsies were examined by three senior pathologists. A clinically significant cancer was defined as follows: Gleason score 3 + 4 or higher or Gleason score 6 with a maximum cancer core length longer than 4 mm [14]. This definition was selected for the figures in an effort to incorporate both grade and volume into the definition of significance. Low-risk PCa on biopsy was defined as Gleason score 6 or low-volume Gleason score 3 + 4 [15, 16]. Intermediate-risk PCa was defined as Gleason score 3 + 4 with 50 % or more of any core positive for cancer or 33 % or more of SB cores positive for cancer. High-risk PCa was defined as Gleason score 4 + 3 or greater cancers [16]. The biopsy-proven index lesion of each patient was defined primarily as the lesion with the highest Gleason score and secondarily as the lesion with the greatest cancer-involved core in terms of length or percentage [17].

Statistical analysis

Data are presented as the mean ± SD. Statistical analysis involved the use of SPSS 17.0 (SPSS Inc, Chicago, IL). Between-group comparisons involved *t* test and Chi-square test. $P < 0.05$ was considered statistically significant.

Results

All 62 patients were suspected to have PCa with a PI-RAD classification between 2 and 5 according to mpMRI examination. Patient demographics of the study cohort are shown in Table 1. The mean age of the 62 patients was 68.38 ± 6.57 years (range 51–79 years). The mean preoperative PSA value was 10.21 ± 5.57 ng/mL (range 4.5–30.1 ng/mL). The mean preoperative prostate volume, calculated using the ellipsoid formula, was 34.05 ± 9.86 mL (range 19–64 mL). Three patients in our study had a recognized palpable nodule in the prostate based on digital rectal examination (DRE).

The mean biopsy time, including the MRI–TRUS fusion time and needle punctured time without anesthesia, was 20.98 ± 10.38 min (range 11–53 min). An example of MRI–TRUS registration and location of free-hand transperineal TB of a suspicious area in the right side of peripheral zone is presented in Fig. 1. No post-biopsy complication was noted. The SB and/or TB revealed that 34 patients (34/62 patients, 54.8 %) were positive for PCa. The positive rates of the overlapped lesions of SB and TB cores were 12.35 % (124/1004 cores). The Gleason scores of these lesions were 6.97 ± 0.90 (range 6–9). The positive core length and percent of biopsy cores were 4.42 ± 2.98 mm (range 1–17 mm) and 32.60 ± 19.61 % (range 7–100 %), respectively. The results of the prostate biopsies are also shown in Table 1.

The comparative results of prostate biopsies in SB and TB are shown in Table 2. The SB and TB detected PCa in 21 (33.9 %) and 27 (43.5 %) patients, respectively ($P = 0.27$). The 2 approaches differed in that SB diagnosed 28.1 % more patients with low-risk PCa versus TB (16 vs. 13 men, $P = 0.049$) and TB detected 28.1 % more patients with

Table 1 Patient demographics and summary of biopsy findings

Men, no.	62
Age, year (range)	68.38 ± 6.57 (51–79)
PSA, ng/ml (range)	10.21 ± 5.57 (4.5–30.1)
Suspicious DRE findings	3
Prostate volume, ml (range)	34.05 ± 9.86 (19–64)
PI-RAD scores, *n* (%)	
2	14 (22.6)
3	21 (33.9)
4	16 (25.8)
5	11 (17.7)
MRI lesions per patient, no.	1.97 ± 0.81
Biopsy time, min (range)	20.98 ± 10.38 (11–53)
Men with prostate cancer, no. (%) (target biopsy or systematic biopsy)	34 (54.8 %)
Men with low-risk PCa, no (%)	18 (29.0 %)
Men with intermediate-risk PCa, no (%)	7 (11.3 %)
Men with high-risk PCa, no (%)	9 (14.5 %)
Gleason score (range)	6.97 ± 0.90 (6–9)
Positive core length of biopsy cores (range)	4.42 ± 2.98 mm (1–17)
Positive core percent of biopsy cores (range)	32.60 ± 19.61 % (7–100)
Biopsy cores per patient	15.94 ± 1.62
Positive lesions on targeted biopsy core (per patient)	2.07 ± 1.14

Continuous variables reported as mean ± standard deviation

PSA prostate-specific antigen, *DRE* digital rectal examination, *mpMRI* multiparametric magnetic resonance imaging, *MRI* magnetic resonance imaging

Table 2 Results of prostate biopsies in systematic and targeted cores

	Systematic biopsy (SB) cores	Targeted biopsy (TB) cores	*P* value
Men with positive biopsies, no. (%)	21 (33.9 %)	27 (43.5 %)	0.27
Men with low-risk PCa, no. (%)	16 (76.2 %)	13 (48.1 %)	0.049
Men with intermediate-risk PCa, no. (%)	2 (9.5 %)	6 (22.2 %)	0.242
Men with high-risk PCa, no (%)	3 (14.3 %)	8 (29.6 %)	0.210
Men with intermediate-risk and high-risk PCa, no. (%)	5 (23.8 %)	14 (51.9 %)	0.049
Total biopsy cores, no	744	260	–
PCa of biopsy cores, no (%)	56 (7.53 %)	68 (26.2 %)	<0.001
Positive core length of biopsy cores (range)	3.71 ± 2.77 (1–14 mm)	5.00 ± 3.04 (2–17 mm)	0.016
Positive core percent of biopsy cores (range)	28.77 ± 20.13 % (7–100 %)	35.76 ± 18.73 (11–100 %)	0.048
Primary Gleason grade of biopsies (range)	3.34 ± 0.48 (3–4)	3.57 ± 0.50 (3–4)	0.009
Secondary Gleason grade of biopsies (range)	3.46 ± 0.50 (3–4)	3.59 ± 0.63 (3–5)	0.225
Gleason score of biopsies (range)	6.80 ± 0.67 (6–8)	7.16 ± 0.86 (6–9)	0.012
Clinically significant PCa cores, no (%)	19 (2.6)	48 (18.5)	<0.001
Clinically insignificant PCa cores, no (%)	37 (5.0)	20 (7.7)	0.103

Continuous variables reported as mean ± standard deviation

PCa prostate cancer

intermediate-risk and high-risk PCa versus SB (14 vs. 5 men, $P = 0.049$) (Table 2). For the SB and TB cores, the total numbers were 744 cores and 260 cores, respectively. The evaluation of biopsy cores revealed that 56/744 cores (7.53 %) on SB were cancer positive, while 68/260 cores (26.2 %) on TB were cancer positive ($P < 0.001$). Thus, the detection rate was significantly higher in TB compared to that in SB. The positive core length of SB and TB cores was 3.71 ± 2.77 mm (range 1–14 mm) and 5.00 ± 3.04 mm (range 2–17 mm), respectively ($P = 0.016$). The positive core

Table 3 Additional utility of targeted biopsy over systematic biopsy alone and of systematic biopsy over targeted biopsy alone

	PCa clinical significance		Total
	Insignificant, no.	Significant, no.	
PCa cases diagnosed by SB	14	7	21
Additional PCa cases diagnosed by TB	4	9	13
Additional percent of PCa missed by SB (%)	22.2	56.3	38.2
PCa cases diagnosed by TB	11	16	27
Additional PCa cases diagnosed by SB	4	3	7
Additional percent of PCa missed by TB (%)	26.7	15.8	20.6

PCa prostate cancer, *SB* systematic biopsy, *TB* targeted biopsy

percent of SB and TB cores was 28.77 ± 20.13 % (range 7–100 %) and 35.76 ± 18.73 (range 11–100 %), respectively ($P = 0.048$). Moreover, the primary Gleason grade of biopsies detected by SB and TB was 3.34 ± 0.48 (range 3–4) and 3.57 ± 0.50 (range 3–4), respectively ($P = 0.009$). The secondary Gleason grade of biopsies detected by SB and TB was 3.46 ± 0.50 (range 3–4) and 3.59 ± 0.63 (range 3–5), respectively ($P = 0.225$). The Gleason scores of biopsies detected by SB and TB were 6.80 ± 0.67 (range 6–8) and 7.16 ± 0.86 (range 6–9), respectively ($P = 0.012$). The rates of the detection of biopsy-proven clinically significant ($P < 0.001$) and insignificant PCa ($P = 0.103$) in SB and TB were 7.7 and 18.5, and 5.0 and 2.6 %, respectively.

Discussion

The present results showed that cancer detection rate when using TB was significantly better than when using 12-core SB ($P < 0.001$) (Table 2). Positive core length, positive core percent, primary Gleason grade, Gleason score, and detection rate of clinically significant PCa were also significantly different between SB and TB (all $P < 0.05$) (Table 2). Based on our results, it is indicated that the free-hand transperineal TB guided by mpMRI–TRUS fusion images had the ability to improve sampling quality and detect more clinically significant PCa (Table 3) compared to SB.

Prostate biopsy guided by TRUS is routinely performed for the diagnosis of PCa. With the current standard of including 10–14 randomized cores, the cancer detection rate in first-time biopsy cases has been reported to be 20–40 % [4]. Even in these patients who underwent saturation biopsy, the cancer detection rate is only 30–45 % [18]. Thus, these conventional biopsy techniques not only are suboptimal in detecting PCa, but also suffer from complications associated with obtaining a large number of biopsy cores [19].

The potential of prebiopsy MRI is recently highlighted in a European consensus meeting [20] and in the 2012 European Society of Uroradiology guidelines [11]. However, the disadvantage of MRI is that it is not real time and cannot be used for observation during biopsy of the prostate. MR-guided biopsy approaches have been reported in the literature [21]; however, their techniques have several difficulties. Open MR scanners do not provide optimal tissue contrast, thus suffering from registration problems, and closed MR scanners require expensive MRI-compatible biopsy instrument [8].

Real-time fusion of TRUS and MRI images of the prostate is feasible and potentially able to identify regions of cancer for subsequent biopsy, which can be performed using MRI localization information without requiring the cost, difficulties, or inconvenience of an MRI suite or MRI-compatible equipment. The greatest increase in cost is due to the MRI performed on each patient. In the dilemma between under-diagnosis of significant PCa, and over-diagnosis and subsequent overtreatment of clinically low-risk tumors, TB may offer significant improvement [20, 22]. Recently, studies suggest that TB achieves equivalent or superior detection of significant cancer with fewer cores and less over-detection [13, 23–26]. In this study, we used the mpMRI for PCa detection and fused mpMRI images to the images of TRUS by RVS® provided by Hitachi Medical Corporation. As shown in Fig. 1, a suspicious area of PCa on the right side of the prostate peripheral zone was detected by prebiopsy mpMRI examination. However, we found that this suspicious area detected in mpMRI was not obvious in the images of TRUS. The operator free hand transperineally inserted the needle (Fig. 1b) guided by real-time fusion imaging of mpMRI and TRUS, and could obtain the prostate specimens by viewing the sagittal image of the prostate (Fig. 1c). This MRI–TRUS fusion-guided prostate biopsy of the patient revealed Gleason 4 + 4 tumor in this lesion (95 % core involvement). It is indicated that mpMRI had the advantage of recognizing clinically significant PCa compared to TRUS.

From the results of our study, the cancer detection rate was significantly higher in TB cores (26.2 %) compared to that in SB cores (7.53 %) ($P < 0.001$). Moreover, the positive core length, positive core percent, and primary Gleason grade of TB cores were improved significantly compared to that in SB cores. The detection rate of low-risk PCa by SB was significantly higher than that by TB ($P = 0.049$); however, the detection rate of intermediate-risk and high-risk PCa by SB was significantly lower than that by TB ($P = 0.049$) (Table 2). These data indicated that TB guided by mpMRI–TRUS fusion imaging had the ability to improve the PCa detection rate and biopsy samples quality. Moreover, we found that the cores of

clinically significant PCa detected by TB were significantly more than cores detected by SB. It is indicated that TB guided by mpMRI–TRUS fusion imaging was superior to the method of 12-core SB for clinically significant PCa and intermediate-risk and high-risk PCa detection (Table 3).

As we all know, the incidence of infectious complications following TRUS-guided transrectal approach for prostate biopsy is gradually, but steadily increased. It is reported that the incidence of post-TRUS-guided transrectal approach for prostate biopsy sepsis has been as high as 5 % [27]. There was an increased interest in the use of a transperineal approach for prostate biopsy in recent times [28]. Transperineal prostate biopsy has the advantage of avoiding penetration of the rectal mucosa and thus minimizing inoculation of the prostate with bowel flora. Of the many published series of transperineal prostate biopsy experience, the incidence of sepsis is either zero or close to zero and non-life-threatening urinary tract infections are uncommon [28, 29]. In this study, we use the biopsy methodology of transperineal prostate biopsy and no post-procedure complication including infectious complications was noted. However, the number of patients in our study was too small and needed further follow-up.

It is reported that free-hand procedure is a cheaper, faster, and more accessible solution for prostate biopsy compared to template biopsy [30]. Free-hand prostate biopsy just needs a standard transrectal ultrasound unit and probe. It could vastly reduce the resources required and the time taken to perform the procedure in comparison with a template biopsy [30]. Our own experience of free-hand transperineal targeted prostate biopsy with real-time fusion imaging of mpMRI and TRUS is limited, and we would acknowledge that it is a difficult technique to acquire and needs a learning curve. Passing a needle accurately to the suspicious areas without a needle guide takes skill, and sampling the base of the prostate, particularly in large glands, is more difficult than with a transrectal technique.

The present study has several limitations. First, the reproducibility of the TRUS findings depends on operator skill. Therefore, standardization of TRUS techniques is required for successful biopsy. Next, the present study did not compare biopsy results with pathological findings from whole-gland specimens. Therefore, it is difficult to exclude the possibility that a clinically important cancer has been missed without pathological analysis of whole-gland specimens. Third, the number of the patients included in the present study was too small to evaluate the accurate cancer detection rate of the system.

Conclusion

This single-center clinical study in China showed encouraging results and the feasibility of free-hand transperineal targeted biopsy guided by real-time fusion imaging of mpMRI and TRUS. This device provides guidance to predefined MRI targets with promising results in terms of total and clinically significant PCa detection and biopsy sample quality. Further study of the comparisons between the pathological findings of whole-gland specimens will give a larger role to the present biopsy method, such as in patient selection of focal therapy and precise per-lesion follow-up under active surveillance.

Conflict of interest We have no financial disclosures to declare and no conflicts of interest to report.

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