Asian Journal of Andrology (2020) 22, 432–436
www.asiaandro.com; www.ajandrology.com

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ORIGINAL ARTICLE

Prostate Cancer

Initial experience with a novel method for cognitive transperineal magnetic resonance imaging-targeted prostate biopsy

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A cognitive magnetic resonance imaging (MRI)-targeted prostate biopsy conducted by an experienced clinician enhances the detection rate of (high-grade) prostate cancer; however, this method is less successful in the hands of inexperienced surgeons. Therefore, an alternative method of conducting a cognitive MRI-targeted biopsy that can be successfully performed by the inexperienced clinicians should be developed. Ninety-six males suspected of prostate cancer were analyzed using systematic biopsy and cognitive MRI-targeted biopsy based on our novel three-dimensional matrix positioning method. Typically, the core principle of the latter procedure was to put the MRI and ultrasound images into the same virtual coordinate system. Afterward, the targeted biopsy was transformed to target a coordinate for the suspected lesion in the MRI. Subsequently, patients were assessed for the presence/absence of prostate cancer or high-grade prostate cancer. According to our results, the overall detection rate of prostate cancer was 70.8% (68/96), and the detection rate of high-grade prostate cancer was 56.3% (54/96). Specifically, the detection rate of prostate cancer by systematic biopsy was 54.2% (52/96) and that by targeted biopsy was 59.4% (57/96; $P = 0.560$). Clearly, the combined application of targeted biopsy could remarkably increase the detection rates of prostate cancer ($P = 0.025$) and high-grade prostate cancer ($P = 0.009$). Taken together, the findings of this study suggest that the combination of systematic biopsy with our three-dimensional matrix positioning-driven cognitive-targeted biopsy is superior to systematic biopsy in detecting prostate cancer and high-grade prostate cancer.

Asian Journal of Andrology (2020) **22**, 432–436; doi: 10.4103/aja.aja_83_19; published online: 27 August 2019

Keywords: cognitive fusion; targeted biopsy; three-dimensional

INTRODUCTION

Prostate cancer is the most commonly diagnosed noncutaneous malignancy, which also is the second leading cause of cancer-related death in men worldwide.[1] Prostate cancer can be diagnosed based on systematic prostate biopsy. Guidelines from the European Association of Urology recommend that patients who meet the indications for biopsy should receive a transrectal ultrasound-guided extended and systematic 10–12-core biopsy.[2] However, such a random sampling strategy may fail to detect prostate cancer,[3] which may also be ineffective at assessing the disease aggressiveness.[4] Multiparametric magnetic resonance imaging (MRI) may increase the diagnosis rate of clinically significant prostate cancer and assist in identifying the location of the suspected lesion.[5] Notably, in-bore MRI-guided biopsy can detect disease at a higher rate than that of systematic biopsy. In addition, the combination of MRI with ultrasound may further increase the detection rate of prostate cancer; to be specific, biopsies that are targeted by the fusion of MRI and ultrasound under the guidance of transrectal ultrasound can achieve a disease detection rate of 34%, which is higher than 27% achievable by systematic biopsy.[6]

However, expensive equipment or specialized software is required for in-bore MRI-guided biopsy and software coregistration fusion biopsy, so performing MRI and real-time ultrasound is restricted in hospitals, particularly in those with limited resources or small caseloads.[7] Under such circumstances, visual estimation (cognitive) fusion techniques may be more practical, which also have an ability of diagnosing any prostate cancer and clinically significant prostate cancer similar to the expensive options.[8,9] However, such approaches require considerable skills and are often effective only in the hands of experienced clinicians.[7]

In this study, a three-dimensional (3D) matrix positioning method was described to assist the surgeons in targeting prostate cancer lesions on ultrasound in a cognitive fusion-targeted biopsy approach. Moreover, its ability to detect any prostate cancer and high-grade prostate cancer was compared with the performance of systematic biopsy.

PATIENTS AND METHODS

Study population

This study was approved by the Research Ethics Committee of Shanghai Changhai Hospital (Shanghai, China), and 96 men with clinically

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Received: 14 October 2018; Accepted: 16 June 2019

suspected prostate cancer and adequate clinical information treated at Shanghai Changhai Hospital between April 2014 and February 2017 were enrolled. Written informed consent was obtained from every patient. All participants underwent multiparametric MRI using a 1.5- or 3.0-T device, followed by MRI-based transperineal ultrasound-guided prostate biopsy. Data for all patients were prospectively collected and retrospectively reviewed. Two radiologists with over 10 years of MRI experience (Qing-Song Yang) were responsible for evaluating and rating the images according to the Prostate Imaging Reporting and Data System (PI-RADS).[10] The clinically significant disease was defined as high-grade prostate cancer (Gleason score of ≥7).

Biopsy

Prostate biopsies were performed in accordance with standard procedures using a biopsy gun (Magnum MG15-22; Bard, Tempe, AZ, USA) equipped with a biopsy needle (18G, 130; Bard) under the guidance of a Flex focus 800 ultrasound device (Peabody, MA, USA) equipped with a bi-planar transrectal transducer (8848, BK Ultrasound, Peabody, MA, USA). The biopsy was performed under freehand without the guidance of a template or any other auxiliary tools.

Cognitive fusion-targeted biopsy aided by a novel 3D matrix positioning method

In this method, transperineal prostate biopsy was performed under the guidance of transrectal ultrasound. During this procedure, the z-axis was defined as the vertical axis of the prostate, the x-axis was the horizontal line on the prostate axial plane, and the y-axis was the vertical line of the x-axis on the axial plane. Typically, these three axes were used to define the locations of the suspected lesions based on MRI. The z-axis coordinate was determined by calculating the distance from the apex level to the proximal ejaculation duct level (**Figure 1**).

The 3D axis coordinates were used to identify the lesion location under the guidance of ultrasound as follows. The transverse sagittal plane with the suspected lesion was confirmed based on the z-axis coordinate calculated previously from MRI. Furthermore, the axial plane with the suspected lesion was determined according to the x- and y-axis coordinates calculated from MRI (**Figure 1**).

Based on the matrix points derived from ultrasound images, the needle could be penetrated into the suspected lesion site, and its direction should be adjusted toward the suspected lesion (**Figure 1**); subsequently, the puncture gun was triggered. A real case is presented in **Figure 2**.

Statistical analyses

Data were analyzed using SPSS 15.0 (IBM, Armonk, NY, USA). Categorical data were compared between groups using the Chi-square or Fisher's exact test, while continuous data were compared by Student's *t*-test or the Mann–Whitney U test. All *P* values were two-sided, and a difference of $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 96 patients were enrolled in this study. Among them, 64 (66.7%) were naive to biopsy, and the remaining 32 (33.3%) had received at least one negative biopsy previously. The clinical information of the enrolled patients is illustrated in **Table 1**. As could be observed, the median age of patients was 67 years. Furthermore, there were 44 (45.8%) patients with a prostate-specific antigen (PSA) level of <10 ng ml^{-1}, 42 (43.8%) of 10–20 ng ml^{-1}, and 10 (10.4%) of 20–30 ng ml^{-1}, yielding the median PSA level of 10.48 ng ml^{-1}. Sextant or 12-core systematic biopsies were performed in all patients, and a

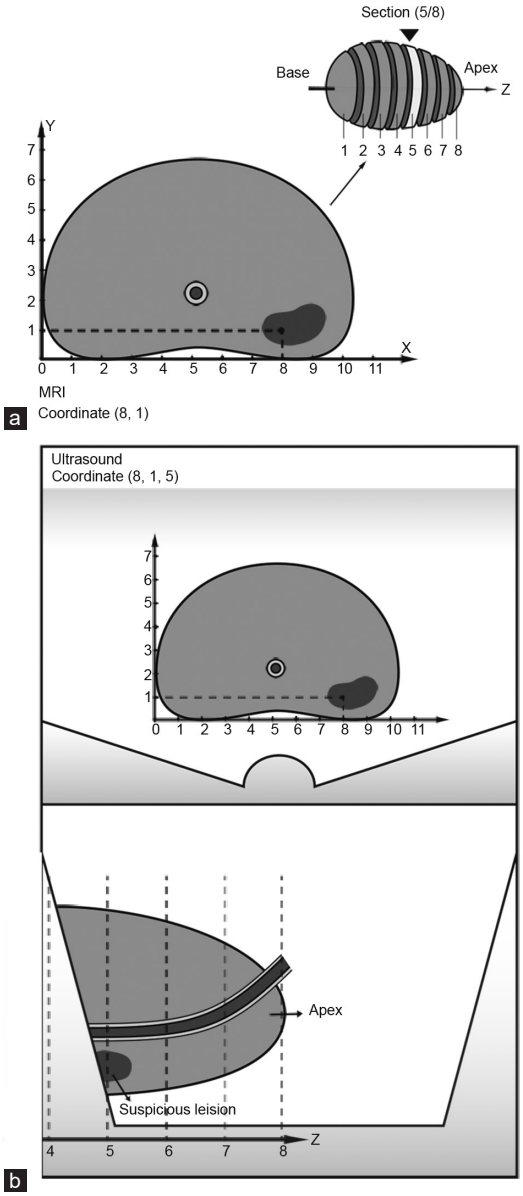

Figure 1: Schematic diagram of cognitive fusion targeted biopsy aided by a novel 3D matrix positioning method. (**a**) The 3D matrix in an MRI image. The MRI showed a suspicious lesion in the left peripheral zone, middle of the gland. A cognitive 3D matrix was developed based on the MRI image, the direction of the x-axis was from right to left of the sectional plane of the gland and the y-axis was from posterior to anterior. In addition, the direction of the z-axis was from base to apex of the sagittal plane of the gland. The suspicious lesion was located from 7.5 to 9.5 in the x-axis (range: 0–10.5), from 0.5 to 2 in the y-axis (range: 0–6.5) and 5 in the z-axis (range: 1–8). The coordinate of the suspicious lesion was (7.5–9.5, 0.5–2, 5) in the 3D matrix position. (**b**) The 3D matrix in an ultrasound image. The suspicious lesion was found in the bi-planar ultrasound image according to the 3D matrix, which was developed from the MRI image. MRI: magnetic resonance imaging; 3D: three-dimensional.

median biopsy core of three was applied for each suspected lesion on MRI, in accordance with the consensus of the American Urological Association (AUA) and the Society of Abdominal Radiology (SAR) to take at least two cores (**Table 1**).[11]

A total of 105 lesions were observed, with PI-RADS scores of 3–5. Specifically, 89 patients had only one suspected lesion and seven

had two suspected lesions; furthermore, 33 patients had lesions with a PI-RADS score of 3, 38 with a score of 4, and 25 with a score of 5. In addition, the lesion diameter ranged from 0.2 cm to 2.4 cm, with a median of 1.0 (interquartile range [IQR]: 0.7–1.2) cm, and the median estimated lesion size was 0.56 (IQR: 0.33–1.03) cm^2.

Detection rates of prostate cancer and high-grade prostate cancer

The overall detection rate of prostate cancer was 70.8% (68/96; **Table 2**); specifically, the detection rate by systematic biopsy was 54.2% (52/96) and that by targeted biopsy alone was 59.4% (57/96; $P = 0.560$). Clearly, a combination of targeted biopsy and systematic biopsy remarkably increased the detection rate of prostate cancer compared with that by systematic biopsy alone (72.9% [70/96] *vs* 56.3% [54/96]; $P = 0.025$). Moreover, 16 of the 68 (23.5%) prostate cancer cases were missed by systematic biopsy, and 11 of 68 (16.2%) cases, including six cases with high-grade prostate cancer, were missed by targeted biopsy alone.

The overall detection rate of high-grade prostate cancer was 56.3% (54/96). Specifically, the detection rate by systematic biopsy was 36.5% (35/96) and that by targeted biopsy was 46.9% (45/96, $P = 0.188$). It was obvious that the combined application of targeted biopsy and systematic biopsy evidently enhanced the detection rate of high-grade prostate cancer relative to that by systematic biopsy alone ($P = 0.009$). Nineteen (35.2%) high-grade prostate cancer cases were missed by systematic biopsy alone, and nine (16.7%) were missed by targeted biopsy alone ($P = 0.048$).

In patients with prior negative biopsies, the detection rate of prostate cancer was 65.4% (17/26) while that of high-grade prostate cancer was 42.3% (11/26). Among this subgroup of prostate cancer patients, the prostate cancer detection rate by targeted biopsy (53.8%, 14/26) was higher than that by systematic biopsy (26.9%, 7/26). **Table 3** compares the diagnostic performance between targeted biopsy and systematic biopsy.

Detection rates of prostate cancer and high-grade prostate cancer as a function of the PI-RADS score

The detection rate achieved using targeted biopsy was 39.4% (13/33) among patients with an overall PI-RADS score of 3; of them, 81.1% (30/37) had an overall score of 4 and 69.2% (18/26) had an overall score of 5. Notably, the detection rate of targeted biopsy with a PI-RADS score of 3 was lower than that with a PI-RADS score of 4 ($P < 0.01$ for a PI-RADS score of 4 and $P = 0.020$ for a PI-RADS score of 5, respectively). However, there was no significant difference between the PI-RADS scores of 4 and 5 ($P = 0.277$). Similar results were observed from the per-lesion PI-RADS score (**Table 4**).

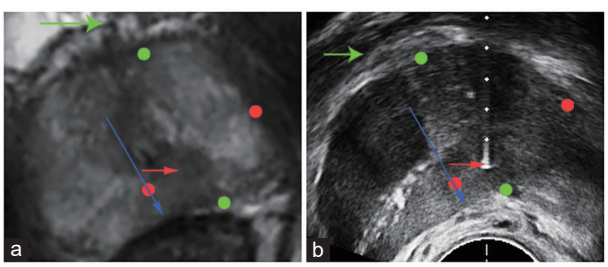

Figure 2: Representative (**a**) T2-weighted magnetic resonance image and (**b**) ultrasound image of the prostate in a patient. The red arrow indicates the suspected lesion in the prostate; the green arrow shows the public bone; and the blue arrow identifies the mid-line of the prostate in the axial plane. The x-axis (red dots) and y-axis (green dots) extend across the center of the suspected lesion. In this patient, the lesion was located in the prostate's posterior third of the y-axis and along the inside third of the x-axis. In the ultrasound image, we first identified the red arrow and the green arrow, then we identified the x- and y-axes based on the relative location of the blue arrow. The lesion was then located in the MRI image in the prostate's posterior third of the y-axis and inside third of the x-axis. MRI: magnetic resonance imaging.

Detection rates of prostate cancer and high-grade prostate cancer as a function of lesion size

The median size across all the 103 MRI lesions was 0.57 (IQR: 0.33–1.04) cm^2, with 0.62 (IQR: 0.38–1.04) cm^2 for the positive

Table 1: Patient baseline information

Clinical characteristics	*Value*
Age (year), median (IQR)	67 (62–73)
Total PSA (ng ml^{-1}), median (IQR)	10.48 (7.03–16.25)
%fPSA, median (IQR)	0.12 (0.08–0.18)
Number of suspicious DRE, *n* (%)	24 (25.0)
Prostate volume (ml), median (IQR)	36.63 (23.05–54.70)
Number of prior biopsies, *n* (%)	32 (33.3)
Overall PI-RADS scores, *n* (%)	
3	33 (34.4)
4	37 (38.5)
5	26 (27.1)
Number of TB cores (*n*), median (IQR)	3 (3–4)
Number of SB cores (*n*), median (IQR)	12 (6–12)

IQR: interquartile range; DRE: digital rectal examination; PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen; SB: systematic biopsy; TB: targeted biopsy; %fPSA: percentage of free prostate-specific antigen

Table 2: Comparison of biopsy results from systematic biopsies and magnetic resonance imaging-targeted biopsies

Targeted biopsy	*Systematic biopsy*		*Total*	*Systematic biopsy*		*Total*
	NBx	*PCa*		*Non-HGPCa*	*HGPCa*	
NBx	28	11	39	NA	NA	NA
PCa	16	41	57	NA	NA	NA
Total	44	52	96	NA	NA	NA
Non-HGPCa	NA	NA	NA	42	9	51
HGPCa	NA	NA	NA	19	26	45
Total	NA	NA	NA	61	35	96

NA: not analyzed; NBx: negative biopsy; PCa: prostate cancer; HGPCa: high grade prostate cancer

Table 3: Performance comparison of targeted biopsy and systematic biopsy using combined biopsy as standard reference

Statistical indicator	*Targeted biopsy*	*Systematic biopsy*
Sensitivity	0.80 (0.68–0.88)	0.76 (0.64–0.85)
Specificity	1.00 (0.84–1.00)	1.00 (0.84–1.00)
NPV	0.65 (0.48–0.79)	0.60 (0.44–0.75)
PPV	1.00 (0.92–1.00)	1.00 (0.92–1.00)

NPV: negative predictive value; PPV: positive predictive value

Table 4: Gleason score of systematic biopsies and magnetic resonance imaging targeted biopsies

Gleason score of targeted biopsy	*Gleason score of systematic biopsy*					*Total*
	NBx	*6*	*3+4*	*4+3*	*8 or higher*	
NBx	NA	6	2	0	4	12
6	5	3	1	0	3	12
3+4	3	5	1	1	1	11
4+3	3	2	2	3	1	11
8 or higher	5	1	0	4	12	22
Total	16	17	6	8	21	68

NBx: negative biopsy; NA: not applicable

targeted biopsy cores and 0.47 cm^2 (IQR: 0.29–0.92 cm^2; $P = 0.368$) for the negative targeted biopsy cores.

Comparison of Gleason scores between systematic and targeted biopsy cores

According to systematic biopsy, 17, 6, 8, and 21 cases were identified as having respective Gleason scores of 6, 3+4, 4+3, or ≥8 (**Table 4**); and in targeted biopsy, 12, 11, 11, and 22 cases were recognized as having the above-mentioned Gleason scores, respectively. Less than a half (8/17) of patients with a Gleason score of 6 based on systematic biopsy were found to have a higher Gleason score according to targeted biopsy, resulting in a higher detection rate of high-grade prostate cancer.

DISCUSSION

Cognitive software fusion biopsy has worse performance than in-bore biopsy and software co-registration fusion biopsy in terms of overall detection of prostate cancer[12–14] as well as detection of small and transitional zone lesions.[8] Nonetheless, all these three approaches are associated with similar detection rates of clinically significant prostate cancer. This finding suggests that cognitive fusion-targeted biopsy, which requires no extra equipment, is the most cost-effective approach to detect clinically significant disease. Some studies report that software co-registration performs better than the cognitive approaches for software fusion biopsy, which may reflect the strong dependence of the performance of cognitive approaches on the experience of the clinicians.[15] In this study, a 3D matrix positioning method was described to support cognitive fusion-targeted prostate biopsy, which was also validated in comparison with systematic biopsy alone.

This study showed that the novel 3D positioning method discussed herein might help to identify the location of suspected lesions, with a median size of about 0.5 cm^2. The median lesion size for positive biopsy is larger than that for negative biopsy, but the difference was not statistically significant. This finding seemed to go against the intuition and clinical experience that the lesion size makes a difference, particularly when the lesion size was small. Therefore, it was predicted that there might be some confounding factors in the relationship between the detection rate of prostate cancer and the lesion size, but the exact influence of these variables could not be easily determined because of the limited sample size in this study.

In addition, our study demonstrated that a Gleason score of 6 based on systematic biopsy was not a completely reliable indicator for low-grade prostate cancer. In other words, active surveillance or other conservative treatment might still be required for these patients. These results also suggested that targeted biopsy cores might provide a more accurate diagnosis of the pathological state of prostate cancer patients, which might thereby improve the subsequent treatment. Our method was based on our reasoning that cognitive fusion-targeted biopsy demanded proficiency in anatomy, high-quality ultrasound imaging of the prostate, and good spatial thinking. Of note, our approach enabled inexperienced clinicians to obtain reliable results because the operator could identify the midline of the prostate on the axial plane and then focus the targeted area on this plane based on the x- and y-axis coordinates. This result was in better coincidence of the MRI and ultrasound images. In addition, it was discovered from our study that adding the results of our targeted biopsy approach to those of systematic biopsy could obviously increase the detection rates of both prostate cancer and high-grade prostate cancer. Our findings suggest the potential for developing standard procedures to allow clinicians to apply our method in their environments, in the absence of the specialized hardware or software required in other MRI-targeted biopsy approaches. Experienced clinicians can achieve a high detection rate of prostate cancer using traditional cognitive fusion methods; however, it is difficult for novices to construct a lesion location image based on different MRI and ultrasound images and to precisely puncture the target during the biopsy process. To overcome these weaknesses, our novel 3D positioning method sets up a common frame of reference, which serves as a bridge to connect the two different images, thus assisting clinicians in taking the target lesion "from point to point." Our findings confirmed the superiority of this new method over systemic biopsy. Next, we compare our method with traditional cognitive-targeted biopsy in terms of the detection rate of prostate cancer and the learning curve so as to further assess its clinical value.

Several limitations of this study should be noted. First, patients were not categorized according to the number of prior biopsies, PSA level, or other clinical parameters, because we only intended to assess the effectiveness of our method for sampling suspected lesions. Second, 12-core systematic biopsies were not performed in all patients; in particular, such biopsies were not carried out in patients who had already had negative 12-core systematic biopsies, thus avoiding the risk of unnecessary injury. Third, this cognitive approach was not compared with software-assisted or conventional cognitive approaches to fusion-targeted biopsy. Therefore, further comparison studies are warranted.

CONCLUSION

The findings of this study suggest that cognitive fusion-targeted biopsy, aided by the novel 3D matrix positioning method described in this study, can be used in combination with systematic biopsy to attain higher detection rates of prostate cancer and high-grade prostate cancer than those by systematic biopsy alone.

AUTHOR CONTRIBUTIONS

HFW and RC made substantial contributions to collect the dataset, conceive the study idea, participate in data analysis, conduct statistical analyses, and draft the manuscript. BMH and MQ was involved in drafting the manuscript and revising it critically for important intellectual content, collecting the dataset, and conceiving the study idea. YW and HZL collected the dataset and participated in data analyses. QSY is responsible for the MRI review. BMH has reviewed and polished the manuscript. YHS and XG participated in the study design and coordination. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

ACKNOWLEDGMENTS

This study is supported by the Fund for National Natural Science Foundation Youth Project (No. 81702514, to RC).

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