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Prostate cancer detection by targeted prostate biopsy using the 3D Navigo system: a prospective study

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Abstract

Purpose The 3D Navigo™ system is a magnetic resonance imaging (MRI) and transrectal ultrasound (TRUS) fusion device for prostate targeted biopsies (TB). Our aim was to evaluate the clinically significant prostate cancer (CSC) detection rate of TB using the 3D Navigo™ system.

Methods Patients who underwent TB with the 3D Navigo™ system in our center between June 2014 and May 2018 were prospectively included, excluding those who have previously received treatment for prostate cancer. A 3-Tesla MRI imaging was performed before biopsies; findings were reported according to the Prostate Imaging Reporting and Data System version 2 (PIRADS). CSC was defined by an ISUP score ≥ 2.

Results 304 patients underwent TB. Median age was 66 years (51–84). Median PSA was 7.75 ng/ml (0.6–70.0). Median prostate volume was 45.0 ml (15.9–221.7). PCa and CSC were found in 70.4% (214/304) and 47.7% (145/304) of the patients, respectively. The proportion of patients diagnosed with CSC among those with PCa was 67.8% (145/214). There was a significant risk of having a CSC in case of PIRADS score ≥ 4 and 5 (OR 5.0, 95% CI [2.7–9.2], $P < 0.001$; OR 3.2, 95% CI [1.8–5.5], $P < 0.001$). PIRADS score was an independent risk factor of having a CSC (OR 4.19, 95% CI [2.49–7.05], $P < 0.001$). There was no significant difference between pathological outcomes of TB and RP in paired analysis ($P = 0.892$). There was a correlation between TB and RP specimens for PCa detection ($r = 0.60$, $P < 0.001$).

Conclusion Detecting CSC with MRI-TRUS fusion targeted biopsies using the 3D Navigo™ system is feasible and safe. We found a positive correlation between TB and RP for ISUP scores.

Keywords Prostate cancer · Targeted biopsies · Clinically significant prostate cancer · Fusion biopsy · PIRADS version 2 score

Introduction

Prostate cancer (PCa) is the most frequently diagnosed neoplasm among men [1]. In recent years, multi-parametric magnetic resonance imaging (mpMRI) has become a key element in detecting prostate clinically significant cancers (CSC) [2–6]. Major randomized controlled trials (RCT) such as the PRECISION [5] and the PROMIS trials [7] have demonstrated that targeted biopsies (TB) were superior to systematic biopsies (SB) in detecting CSC. Other studies such as the MRI-FIRST [4] and the 4 M trials [6] have at least demonstrated the added value of performing TB in addition to SB. Therefore, it is now recommended to perform mpMRI before prostate biopsies [8]. TB can be performed cognitively by visual registration, or under direct in-bore MRI guidance or with an MRI/transrectal ultrasound (MRI-TRUS) fusion software [9]. The optimal guiding method for TB has still not been defined [10].

MRI-TRUS fusion registration can be either rigid or elastic [11]. Rigid registration suffers from translation and rotational variations between images, while elastic registration compensates local deformation caused by the TRUS probe.

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No significant difference in PCa detection has been reported between these methods [10].

The Navigo™ workstation (UC-CARE Navigo™ Workstation, Model: FPRMC0016A, Yokneam, Israel) is an easy-to-use MRI-TRUS elastic fusion device designed to assist the physician in performing TB. The device uses an external electromagnetic tracking system and a software-based registration algorithm, which compensates for patient body and prostate motion during the whole procedure. It also allows real-time visualization of the prostate, the needle and the biopsy cores. Three preliminary studies have shown the feasibility of a 3D modelization of the prostate using the Navigo™ system [12–14]: recently, Gayet et al. reported a retrospective study on an older version of the Navigo™ system, considering only the TRUS-guided capacity of the platform in performing prostate biopsies; however, they did not use MRI/US fusion [12]. The present study is the first one to assess the 3D Navigo™ system for MRI-TRUS TB.

The primary objective was to evaluate the clinically significant prostate cancer detection rate of TB using the 3D Navigo™ system.

Materials and methods

We prospectively included all patients who underwent MRI-TRUS fusion TB using the 3D Navigo™ system in our center between June 2014 and May 2018.

During this period, all patients undergoing prostate cancer screening or active surveillance who needed biopsies had an mpMRI first. TB using the 3D Navigo™ system were systematically performed in all patients with suspicious lesions identified on mpMRI (PIRADS score ≥ 3). No systematic biopsies were performed. Patients with a history of radiotherapy, brachytherapy and vascular-targeted photodynamic therapy were excluded. CSC on TB was defined by an ISUP score ≥ 2. CSC was defined on radical prostatectomy (RP) specimen by an ISUP score ≥ 2 or a T-stage ≥ 3.

This study has been ethically approved by the French National Commission for Data Protection – Registration number: 2019-004 (CNIL).

MpMRI protocol

All prostate mpMRIs were performed on a 3T Magnetum Skyra (Siemens) using a pelvic coil. The mpMRI protocol included T2-weighted images, DWI and DCE sequences. T2-weighted images were acquired in axial, coronal and sagittal plane (the coronal plane passing through the seminal vesicles and the axial plane was orthogonal to the coronal plane). The axial plane had 3 mm thick slices (true resolution: $0.7 \times 0.7 \times 3$ mm, FOV 180, Matrix 250×250), the coronal and sagittal planes had also 3 mm thick slices (true resolution: $0.63 \times 0.63 \times 3$ mm, FOV 200, Matrix 320×320). DWI included 0, 50, 500, 1000 and 2000 *b*-values. Contrast enhanced dynamic imaging was obtained after intravenous injection of a bolus of gadolinium chelates at a dose of 0.1 mmol/kg of bodyweight. Both high b-value images and ADC map were analyzed. DCE sequence had a 7.5 s temporal resolution. MRI reports were provided by an experienced radiologist with a urologic imaging expertise of 13 years. The mpMRI analysis was based on V1-PIRADS scoring from 2014 to 2015 and on V2-PIRADS scoring system with diagrammatic report after 2015 [13] and was compliant to the Standards of reporting for MRI-targeted biopsy studies (START) Working Group guidelines [14]. The PSA value and the rectal examination result were provided to the radiologist.

Biopsy protocol

Biopsies were performed by a single surgeon specialized in prostate cancer management and previously trained with the device. The Navigo™ workstation (UC-CARE Navigo™ Workstation, Model: FPRMC0016A, Yokneam, Israel), coupled with the BK Medical PRO FOCUS ultrasound machine (BK Medical, Herlev, Denmark) was used to perform the prostate biopsies. The US probe was an endorectal biopsy probe (type 8818—BK Medical, Herlev, Denmark), with an operating bandwidth of 12-4 MHz. At first, the images of the 3-Tesla mpMRI were analyzed on the workstation. Contouring was performed on T2-weighted images in the axial planes. An electromagnetic tracking system including a transmitter, and two miniature sensors were used (one sensor attached to the ultrasound probe, another attached to the patient's back over the L5 vertebra, and the transmitter was positioned 15 cm above the pelvis). Electromagnetic interference was limited during the procedure.

TRUS images of the whole prostate were acquired by scanning the gland from base to apex in the transversal plane view. Contouring of the prostate and the lesion on the mpMRI images was performed by the radiologist. Contouring of the prostate on the TRUS images was performed by the surgeon. Once the contouring of the prostate on both mpMRI and TRUS images was achieved, elastic fusion was performed. A real-time 3D model was displayed during the rest of the procedure. Local anesthesia was performed by a transrectal periprostatic block. Suspicious lesions and real-time location of the needle were displayed on the real-time 3D model of the prostate during the procedure. All suspicious lesions were biopsied. The number of cores per patient was at the discretion of the practitioner. The location of the biopsy cores was displayed and recorded by the system. An 18-gauge disposable core biopsy instrument (BARD® MAX-CORE, Tempe, Arizona - USA) was used to perform the biopsies. Samples were placed in a stretched

form within a cassette placed in a formaldehyde solution before pathological analysis. The samples were analyzed by 3 different pathologists, with 15 years of experience in the urologic field.

Collected data

The following data were collected: age, PSA, digital rectal examination (DRE) data, treatment by 5α-reductase inhibitor, past history of prostate biopsy, TRUS prostate volume measurement, mpMRI PIRADS score, total number of cores, number of positive biopsies, tumoral infiltration rate (total length of the tumor/total length of the cores), extra prostatic extension, median maximum tumoral length for positive biopsy, ISUP score, side effects, pathological prostatectomy outcomes (including: lesion location and size, pT stage, ISUP score).

Data analysis

The results were expressed as median (interquartile range (IQR)) values. Statistical analysis was performed with the SPSS15.0 Software® (IBM Corp., Armonk, NY, USA). Qualitative and quantitative variables were compared using χ^2 and Wilcoxon tests. The Spearman rank correlation test was used to assess the correlation between the mpMRI and pathological findings. Statistical significance was defined as a $P < 0.05$. Logistic regression was used for multivariable analyses.

Results

Between June 2014 and May 2018, 304 patients underwent TB. Baseline characteristics and biopsy indications are presented in Table 1.

In total, 214 (70.4%) patients were diagnosed with PCa and 145 (47.7%) with CSC. The proportion of patients with CSC among all cancers was 67.8%.

The median number of targeted cores was 9 (IQR 8–12) per patient. The median rate of positive cores per patient was 25% (IQR 0–89%). The median rate of positive cores according to the PIRADS score was 25% (IQR 0–89%), 38% (IQR 0–100%) and 54% (IQR 11–100%) in case of PIRADS score $\geq 3, \geq 4$, and $= 5$, respectively. The median maximum tumoral length for positive cores was 8 mm (IQR 5–11). The median tumoral infiltration rate for positive biopsies was 27% (IQR 10–48%). PCa and CSC detection rates and pathological outcomes according to the PIRADS score are presented in Table 2.

Table 1 Baseline characteristics

Characteristics	All patients ($n = 304$)
Median age, in years, [range]	66 [51–84]
Median PSA, in ng/ml, [range]	7.75 [0.6–70.0]
Abnormal DRE (%)	95 (31.3%)
Median prostate volume, in ml [range]	45.0 [15.9–221.7]
5α-reductase inhibitor treatment (%)	22 (7.2%)
Patients without prior biopsy (%)	190 (62.5%)
Patients with prior negative biopsy for cancer (%)	19 (6.3%)
Patients with prior positive biopsy for cancer (%)	95 (31.3%)
ISUP score: 1 (%)	89 (29.3%)
ISUP score: 2 (%)	6 (2.0%)
ISUP score: 3 (%)	0 (0.0%)
ISUP score: 4 (%)	0 (0.0%)
ISUP score: 5 (%)	0 (0.0%)
Prostate biopsy indications, n (%)	
Screening (%)	213 (70.1%)
Abnormal DRE (%)	78 (25.6%)
PSA > 4 ng/ml (%)	196 (64.5%)
Confirmatory biopsies (%)	4 (1.3%)
AS protocol (%)	91 (29.9%)

PSA prostate specific antigen, *DRE* digital rectal examination, *ISUP* International Society of Urological Pathology, *AS* active surveillance, *VTP* vascular-targeted photodynamic therapy

There was a significant risk of having a CSC in case of PIRADS score ≥ 4 and 5 (OR 5.0, 95% CI [2.7–9.2], $P < 0.001$; OR 3.2, 95% CI [1.8–5.5], $P < 0.001$).

Moreover, the PIRADS score was an independent risk factor of having a CSC (OR 4.19, 95% CI [2.49–7.05], $P < 0.001$), such as an abnormal DRE (OR 2.7, 95% CI [1.34–5.41], $P = 0.005$). Univariate and multivariate analysis are presented in Table 3.

According to the Clavien–Dindo Classification [15], there were 0.6% (2/304) grade I complications (persistent hematuria 1 month after the procedure), 1.2% (4/304) grade II complications (2 acute prostatitis, 1 acute orchiepididymitis, 1 unrelated lithiasis renal colic in the immediate aftermath of the procedure) and 0.3% (1/304) unrelated grade IVa complication (1 Ischemic stroke).

Patient with positive biopsies underwent either active surveillance (AS) or radical treatment (RT) in 23% (74/304) and 47.7% (145/304) of the cases, respectively. When a RT was required, 83.4% (121/145) underwent radical prostatectomy (RP), 13.8% (20/145) underwent radiotherapy, and 2.7% (4/145) underwent brachytherapy.

Among the patients who initially were under AS for an ISUP 1: 42.9% (39/91) of them were reclassified as an ISUP ≥ 2 after repeated TB. They either continued AS or underwent a RT after TB in 49.5% (45/91) and 38.5%

Table 2 Patient's pathological results according to the PIRADS score

PIRADS score	Percentage of patients (*n*)	Prostate cancer detection rate, % (n)	CSC detection rate, % (*n*)	Percentage of patients according to the ISUP Score (n)				
				ISUP 1 (*n* = 63)	ISUP 2 (*n* = 57)	ISUP 3 (*n* = 49)	ISUP 4 (*n* = 16)	ISUP 5 (*n* = 15)
= 3	12.7% (36/282)	24.3% (9/36)	8.1% (3/36)	16.6% (6/36)	2.7% (1/36)	2.7% (1/36)	0.0% (0/36)	2.7% (1/36)
= 4	53.5% (151/282)	74.2% (112/151)	50.9% (77/151)	23.3% (35/151)	23.9% (36/151)	17.9% (27/151)	6.0% (9/151)	3.3% (5/151)
= 5	33.8% (95/282)	83.2% (79/95)	60.1% (57/95)	23.1% (22/95)	21.1% (20/95)	22.1% (21/95)	7.4% (7/95)	9.5% (9/95)
≥ 3	100% (282/282)	70.9% (200/282)	48.6% (137/282)	22.3% (63/282)	20.2% (57/282)	17.4% (49/282)	5.7% (16/282)	5.3% (15/282)
≥ 4	87.2% (246/282)	77.6% (191/246)	54.5% (134/246)	23.2% (57/246)	22.8% (56/246)	19.5% (47/246)	6.5% (16/246)	5.7% (14/246)

PIRADS Prostate Imaging Reporting and Data System, *CSC* clinically significant cancer, *ISUP* International Society of Urological Pathology

Table 3 Risk factors for finding clinically significant cancer on targeted biopsies: a univariate and multivariate analyses

	OR	95% CI	*P*
Univariate analysis			
PSA	1.04	0.99–1.09	0.113
PIRADS score	3.59	2.31–5.58	< 0.001
Prostate volume	0.97	0.96–0.98	< 0.001
Abnormal DRE	2.94	1.68–5.12	< 0.001
Age	1.03	0.99–1.07	0.074
Multivariate analysis			
PSA	1.04	0.97–1.12	0.286
PIRADS score	4.19	2.49–7.05	< 0.001
Prostate volume	0.97	0.95–0.98	< 0.001
Abnormal DRE	2.7	1.34–5.41	0.005
Age	1.04	0.99–1.09	0.155

DRE digital rectal examination, *CI* confidence of interval, *PSA* prostate specific antigen

(35/91) of the cases, respectively. Four patients were already under AS for an ISUP1 diagnosed on SB before inclusion; they all underwent confirmatory TB: 2 were reclassified as ISUP 2 and 1 as ISUP 5.

We also made a paired analysis of the pathological findings of TB with radical prostatectomy specimens. Among all patients, 121 patients underwent RP; pathological outcomes were available for 109 patients. The ISUP score was equivalent between TB and RP specimen in 47.7% (52/109) of the cases. The TB ISUP score was underestimated in 30.3% (33/109) of the cases and overestimated in 22.0% (24/109) of the cases (Fig. 1). There was no significant difference in ISUP scores between TB and RP in a paired analysis ($P = 0.892$). Moreover, there was a positive correlation between ISUP scores of TB and RP specimen pathological analyses ($r = 0.60$, $P < 0.001$).

MpMRI correctly identified all foci of CSC found on RP specimens in 67.9% of the cases (74/109). Consequently, mpMRI missed at least one distinct focus of CSC in 32.1% of the cases. MpMRI missed at least one distinct focus of non-CSC in 15.6% of the cases (17/109).

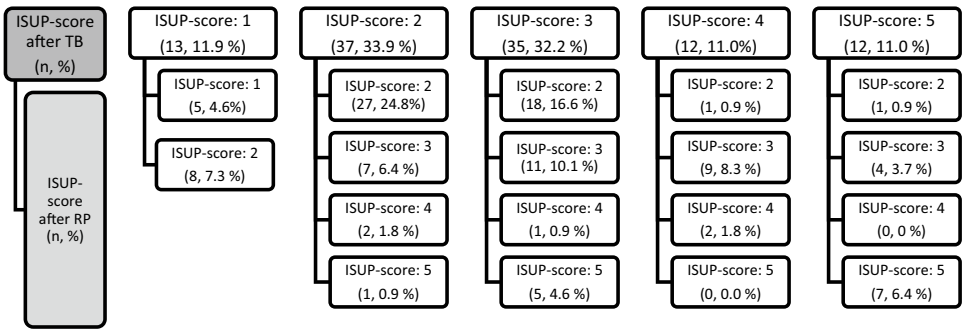

Fig. 1 ISUP score shifts between targeted biopsies and radical prostatectomy. *TB* targeted prostate biopsy, *RP* radical prostatectomy, *ISUP* International Society of Urological Pathology

TB: targeted prostate biopsy, RP: radical prostatectomy, ISUP: International Society of Urological Pathology

Discussion

The detection rates of TB using the 3D Navigo™ system for PCa and CSC were 70.4% and 47.7%, respectively. The proportion of patients with CSC among those with PCa was 67.8%; consequently, only 32.2% had a non-CSC.

In the last 5 years, prostate biopsy procedures have been in constant evolution with the increasing performances of mpMRI in PCa early detection [2, 4, 16]. TB can be performed either cognitively, or under direct in-bore MRI guidance or by MRI-TRUS fusion [9]. On one hand, cognitive fusion is at risk of human error, requiring expertise and rigorous technique [17]; on the other hand, in-bore biopsies are technically challenging, time-consuming and expensive [18]; they also require MRI-compatible equipment which is available in very few centers. Considering this, mpMRI/TRUS fusion technics seem to be very promising. Several mpMRI/TRUS fusion platforms have already been studied [19]. The 3D Navigo™ system is an example of mpMRI/TRUS elastic fusion devices. These devices differ from each other by: the model of the probe, the use of external electromagnetic sensors, the use of robotic technology, and their image processing software. Other elastic MRI-TRUS fusion platforms such as the Koelis Urostation™ system have already been studied: Oderda et al. [20] reported a cancer detection rate of 64% using the Koelis system, with a significantly better detection rate than cognitive TB (40%). According to the systematic review by Gayet et al. the PCa detection rates of the Koelis, Artemis and UroNav systems were: 53.9%, 33.7%, and 50.5%, respectively; the CSC detection rates of the Koelis and the UroNav systems were 43.4% and 44.8%, respectively [19]. That being said, we must be careful when comparing our results to some of these studies because only patients with a positive MRI had biopsies and no systematic biopsies were performed.

Our study provides valuable data on the use of the 3D Navigo™ System for detecting CSC, with a fairly large population and prospectively collected data. The number of cores per patient is consistent with other studies [19, 20]. We reported a high percentage of positive cores of 26%. In comparison, Wysock et al. reported in the PROFUS Trial using the Artemis platform a percentage of positive cores of 5.7%, 13.1% and 16.0% for SB, cognitive fusion biopsies and TB, respectively [21].

The reliability of mpMRI data and the targeting accuracy of the device are critical. For instance, TB may be accurate in targeting a region which was falsely positive at mpMRI; on the contrary, TB might miss a true PCa focus that was correctly defined by mpMRI. To reduce this confounding factor, we used RP specimen outcomes as gold standard references to assess the accuracy of mpMRI in predicting tumor localization [22–24]. In our study mpMRI correctly identified all foci of CSC in 67.9% of the cases. Lee et al. reported that mpMRI missed 20% of CSC foci, which tend to be confirmed by our study although our definitions of CSC differ slightly [25]. However, it is important to keep in mind that the studied population is not a screening population: patients with normal MRIs were not included in the study. Nevertheless, the aim of this study was to evaluate TB using the 3D Navigo™ system in the detection of CSC which can only be performed with an abnormal MRI.

Our results and experience suggest that the 3D Navigo™ system was reliable, and provided a high detection rate of CSC with limited toxicity. However, our study has several limitations. The first one is its monocentric design with a single operator and a single radiologist that may not reflect all technical variations from one center to another. The second limitation was the absence of systematic biopsies in our protocol. This is explained by the fact that our study was designed in 2014: at that time there was not any high-level evidence demonstrating the necessity of combining SB with TB [4, 5, 7]. By the end of the study we of course changed our practice according to the official guidelines [8, 26]. The third limitation was the absence of standard biopsies as a control; however, TB pathological findings were compared to radical prostatectomy pathological findings, which can be considered as a gold standard. Fourth, it should be noted that all results of targeted biopsies were provided at a patient level, but on the contrary, prostatectomy results were provided on a lesion level when confronted to MRI.

Finally, follow-up data were not available in our study, which may limit the clinical significance of negative biopsy findings. A randomized controlled study comparing the 3D Navigo™ system to other targeting systems would be needed. In this study we assessed the transrectal targeted biopsies approach; however, with the proper adjustments, trans-perineal biopsies could be performed if needed with this device.

Conclusion

Detecting clinically significant prostate cancer with MRI-TRUS fusion targeted biopsies using the 3D Navigo™ system is feasible and safe. There was a positive correlation between targeted biopsies and radical prostatectomy pathological outcomes. Further studies are needed to compare the fusion platforms to one another and help practitioners in their choice.

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Declarations

Conflict of interest No authors have any conflicts of interest related to the subject.

Ethical approval This study has been registered by the French National Commission for Data Protection – Registration number: 2019-004 (CNIL).

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