

# 3D Navigo™ versus TRUS-guided prostate biopsy in prostate cancer detection

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## 3D Navigo™ versus TRUS-guided prostate biopsy in prostate cancer detection

Maudy Gayet<sup>1,2</sup> · Anouk van der Aa<sup>1,2</sup> · Peter Schmitz<sup>1</sup> · Harrie P. Beerlage<sup>1,2</sup> · Bart Ph. Schrier<sup>1</sup> · Peter F. A. Mulders<sup>4</sup> · Massimo Mischi<sup>2</sup> · Hessel Wijkstra<sup>2,3</sup>

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### Abstract

**Introduction** To overcome the limitations regarding transrectal ultrasound (TRUS)-guided biopsies in prostate cancer (PCa) detection, there is a focus on new imaging technologies. The Navigo™ system (UC-care, Israel) uses regular TRUS images and electrospatial monitoring to generate a 3D model of the prostate. The aim of this study was to compare cancer detection rates between the Navigo™ system and conventional TRUS, in patients without a history of PCa.

**Methods** We performed a retrospective study by collecting data from all patients who underwent 12-core prostate biopsies from lateral peripheral zones between September 2013 and February 2015 at the Jeroen Bosch Hospital in 's-Hertogenbosch (Netherlands).

**Results** A total of 325 patients met our inclusion criteria. 77.8 % of biopsy sessions were performed using the Navigo™ system. There was no statistically significant difference in PCa detection (39.9 vs 46.2 % with Navigo™

system and TRUS, respectively). Using the Navigo™ system for taking prostate biopsies proved not to be associated with the presence of PCa at biopsy, likewise for clinically significant PCa and for both subgroups.

**Limitations** The limitations of the study include its retrospective design, the limited number of patients in the conventional TRUS group, the statistically significant different number of biopsy sessions and the ones performed by an advanced physician in both groups.

**Conclusion** In our study, there is no added value of 3D TRUS using Navigo™ system compared to conventional 2D TRUS regarding PCa detection in biopsy-naive men and men with prior negative biopsy.

**Keywords** Prostate · Prostate cancer · Ultrasound · 3D · Biopsy

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✉ Maudy Gayet  
M.Gayet@jbz.nl

Anouk van der Aa  
A.v.d.Aa@jbz.nl

Peter Schmitz  
P.Schmitz@jbz.nl

Harrie P. Beerlage  
H.Beerlage@jbz.nl

Bart Ph. Schrier  
B.Schrier@jbz.nl

Peter F. A. Mulders  
Peter.Mulders@radboudumc.nl

Massimo Mischi  
M.Mischi@tue.nl

Hessel Wijkstra  
H.Wijkstra@tue.nl

<sup>1</sup> Department of Urology, Jeroen Bosch Hospital, Post office box 90153, 5200 ME 's-Hertogenbosch, The Netherlands

<sup>2</sup> Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands

<sup>3</sup> Department of Urology, AMC University Hospital, Amsterdam, The Netherlands

<sup>4</sup> Department of Urology, Radboudumc University Hospital, Nijmegen, The Netherlands

## Introduction

Serum prostate-specific antigen (PSA) and digital rectal examination (DRE) are being used in the diagnosis of prostate cancer (PCa). However, definite diagnosis is always based on pathological examination of biopsy cores. Until now, despite limitations, extended systematic transrectal ultrasound (TRUS) biopsies are the gold standard [1]. Cancer detection rates (CDRs) range widely (7.0–38.7 %), depending mainly on the biopsy session number, and nearly 25 % of prostate cancers are missed by the initial biopsy [2, 3]. In addition, there is a poor correlation with pathology after radical prostatectomy. A quarter (20–29 %) of patients who met the active surveillance criteria were diagnosed with unfavourable disease after radical prostatectomy [4, 5]. To overcome these limitations, there is a focus on new imaging technologies. In the last decade, several groups developed 3D TRUS techniques and reported prostate biopsy results using 3D imaging techniques in phantoms [6–9]. Sedelaar et al. [10] published the first clinical study concerning 2D versus 3D TRUS in 2001. A total of 100 patients underwent both 2D and 3D TRUS investigations, and the authors concluded that 3D TRUS did not result in significant improvement in the detection and staging of PCa. Cool et al. [9] compared the biopsy accuracy with 2D TRUS with that of conventional 3D TRUS (unguided) and guided 3D TRUS in a prostate biopsy simulator. Compared with 2D TRUS, the accuracy of biopsies improved with guided 3D TRUS, but did not improve with conventional 3D TRUS (unguided). Peltier et al. [11] published the first clinical study concerning 3D TRUS-guided prostate biopsies using the Urostation (Koelis) in 2013 and concluded that computer-assisted 3D TRUS localization system improves PCa detection rate in clinical practice compared to 2D TRUS-guided systematic biopsy in a comparable cohort of patients and using the same biopsy schemes, with no statistically significant difference when comparing both modalities for potentially clinically insignificant PCa.

In the Jeroen Bosch Hospital ('s-Hertogenbosch, Netherlands), prostate biopsy sessions were conducted using the Navigo™ system (UC-care, Israël) when possible, i.e. the presence of the instructed physician(s) and the absence of a pacemaker or hip prosthesis, since September 2013. Two of 8 (25 %) physicians performing prostate biopsy sessions were trained to use the Navigo™ system by UC-Care, which involved demonstrations and performing 10 biopsy procedures. The Navigo™ system uses regular bi-planar TRUS images and electrospatial monitoring for adjusting movements to generate a 3D model of the prostate and was designed to image and record the locations of prostate biopsy cores. In cases of negative biopsy results and a persistent clinical suspicion of prostate cancer, integrating the

exact locations of previous biopsy cores could be helpful to sample other regions of the prostate. Also it could be helpful to more accurately spread the 10–12 biopsy cores over the gland. The 3D navigation of the biopsy needle towards a fiducial within a prostate phantom using Navigo™ was studied by Cohen [12] and presented in an abstract. In all insertions, the needle tip position was measured within 2–3 mm of the fiducial.

Our hypothesis is that biopsy sessions performed with The Navigo™ system will yield a higher CDR because of a better distribution of the biopsy cores, compared to conventional TRUS. The aim of this retrospective study was to compare the CDRs between the Navigo™ system and conventional TRUS, in patients without a history of PCa.

## Methods

We performed a retrospective study by collecting data from all patients who underwent prostate biopsies from September 2013 until February 2015 at the Jeroen Bosch Hospital in 's-Hertogenbosch (Netherlands). Medical records were consulted for information about the biopsy procedure and pathology results. Inclusion criteria were: PSA between 4 and 10 µg/L, or PSA < 4 µg/L and suspicious DRE. The only exclusion criterion was a history of PCa, for which the patient received either treatment or active surveillance. Clinically significant prostate cancer was defined as Gleason score  $\geq 7$  or at least 2 cores with a Gleason score 6.

## TRUS protocol

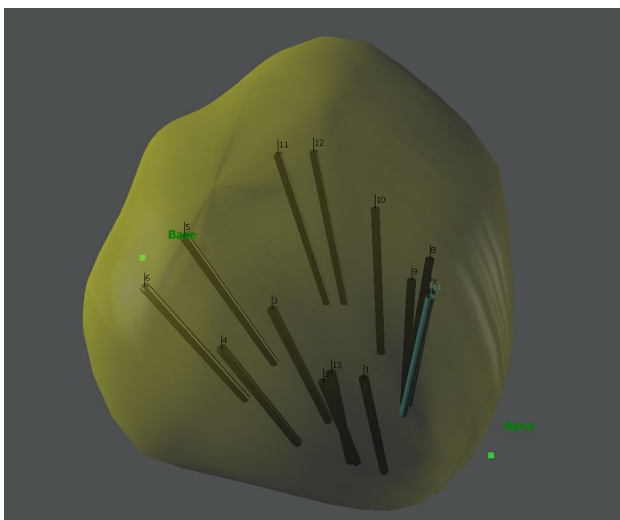
All prostate biopsy sessions were performed with the administration of prophylactic antibiotics (oral ciprofloxacin 500 mg). We started procedures with the patient in left lateral decubitus position. A BK medical ultrasound machine (type 2202) and a sidfire BK Medical probe (type 8808, 6–10 MHz) were used to image the prostate transrectally in transversal and longitudinal views. After volume measurement, a peri-prostatic block was given. A 12-core biopsy protocol in which the lateral peripheral zone was sampled was performed. In case of hypoechogenic lesions outside the regular biopsy areas, 1 or 2 extra cores were taken. Biopsy was performed using a conventional spring-loaded gun with 18-gauge needles. Prostate cores were submitted to the pathology laboratory using the Smart-Bx device. SmartBx™ (UC-care, Israël) is a biopsy core preservation technology, which allows supplying the cores in a stretched form on a cassette. The cassettes are placed within a formaldehyde solution and processed in the pathology laboratory.

## Navigo™ protocol

The Navigo™ protocol is basically similar to the TRUS protocol, only adding some proceedings. The Navigo™ system is used as an adjunct to the ultrasound machine, which means that the same ultrasound machine and probe were used. After prostate volume measurement, the Navigo™ system builds a 3D model. In case of hypoechogenous lesions, these lesions were marked as regions of interest (ROI). During prostate biopsies, both 2D and 3D images were monitored to make sure the right areas were sampled. Navigo™ visualizes the locations of cores taken (see Fig. 1) and shows whether a ROI was correctly sampled.

Descriptive statistics were used to summarize patient characteristics, such as patient age, serum PSA, prostate volume and physician performing the biopsy session. Means and SDs were presented for continuous variables and numbers and percentages for categorical variables. Physicians performing prostate biopsy sessions were split into experienced (more than 10 years experience with prostate biopsy; at least 1500 procedures performed) and less experienced (less than 10 years experience with prostate biopsy). Independent *t* test was used to assess differences between groups for continuous variables, and Pearson Chi-square test was used for categorical variables.

To determine the association between PCa and the biopsy procedure, logistic regression analysis was performed. Both crude and adjusted logistic regression models were constructed. Age, serum PSA, prostate volume, experienced/less experienced physician and performance of prior biopsy were included as independent covariates. A variable was classified as confounder when the resulted variable resulted in at least 10 % change in the regression coefficient when



**Fig. 1** Navigo™ 3D prostate model (yellow), previous biopsy cores in this biopsy session (black) and current biopsy core (blue)

included in the regression model [13]. In addition, possible effect modification was assessed to investigate whether the association between PCa and biopsy procedure is different for different subgroups (e.g. biopsy-naïve men and men after prior negative biopsy). When the *p* value of the interaction term was  $<0.1$ , stratified analyses were performed and the results presented separately for both subgroups. Values of  $p < 0.05$  were considered to be statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

## Results

Between September 2013 and January 2015, we performed 563 prostate biopsy sessions. Of these sessions, 325 sessions met our inclusion criteria, containing 325 different patients. Patients with a PSA  $> 10$   $\mu\text{g/L}$  or patients on active surveillance were disregarded. A total of 253 biopsy sessions (77.8 %) were performed using the Navigo™ system, and the other 72 sessions (22.2 %) were performed using TRUS. Of the 325 biopsy sessions, there were 263 (80.9 %) biopsy-naïve men and 62 (19.1 %) men with prior negative biopsy.

Descriptive statistics are presented in Table 1. Mean patient age was 64.3 years (SD 6.65), mean prostate volume was 50.4 mL (SD 24.16), and mean PSA was 7.0  $\mu\text{g/L}$  (SD 1.771), showing no statistically significant differences between both groups (*p* values 0.300, 0.613, and 0.430, respectively). 64.0 % of all biopsy sessions were performed by our advanced physician, who is also one of the two physicians trained to use the Navigo™ system, and the other 36.0 % by less advanced physicians. Our advanced physician performed 194 of 253 (76.7 %) biopsy sessions using the Navigo™ system and 14 of 72 (19.4 %) biopsy sessions using TRUS, which is a statistically significant difference ( $p = 0.000$ ). CRDs for all PCas were 38.7 and 44.4 % ( $p = 0.383$ ) and CDRs for clinically significant PCas were 23.3 and 30.6 % ( $p = 0.210$ ) in the Navigo™ group and TRUS group, respectively.

Results of logistic regression analyses are presented in Table 2. Crude logistic regression analysis showed no significant association between the use of Navigo™ and the detection of PCa (OR 0.79, 95 % CI 0.466–1.342). The association between the use of Navigo™ or TRUS and PCa was not different for biopsy-naïve men and men after prior negative biopsy ( $p = 0.207$ ); therefore, a sub-analysis for these two groups was omitted. Adjusted logistic regression models were constructed. Age, serum PSA, prostate volume, advanced/less advanced physician and performance of prior biopsy were included as independent covariates. Two variables (prostate volume and advanced/less advanced physician) resulted in a  $>10$  % change in the regression coefficient when included in the regression model, which

**Table 1** Descriptive statistics

	Total	Navigo	TRUS	Sig.
<b>Whole group</b>				
No. of patients	325	253	72	
Mean age in years (SD)	64.3 (6.65)	64.2 (6.52)	64.7 (7.12)	0.300
Mean $\mu\text{g/L}$ PSA (SD)	7.04 (1.771)	7.00 (1.754)	7.17 (1.836)	0.430
Mean mL prostate volume (SD)	50.4 (24.16)	51.0 (24.18)	48.3 (24.15)	0.613
<b>Physician</b>				
No. of advanced (%)	208 (64.0)	194 (76.7)	14 (19.4)	0.000
No. of not advanced (%)	117 (36.0)	59 (23.3)	58 (80.6)	
Presence of PCa (%)	130 (40.0 %)	98 (38.7)	32 (44.4)	0.383
Presence of clinically significant PCa (%)	81 (24.9)	59 (23.3)	22 (30.6)	0.210
<b>Biopsy-naive</b>				
No. of patients	263	204	59	
Mean age in years (SD)	64.4 (6.84)	64.4 (6.76)	64.5 (7.15)	0.385
Mean $\mu\text{g/L}$ PSA (SD)	6.96 (1.773)	6.92 (1.754)	7.09 (1.847)	0.438
Mean mL prostate volume (SD)	49.3 (24.07)	49.4 (23.54)	49.0 (26.06)	0.806
<b>Physician</b>				
No. of advanced (%)	169 (64.3)	157 (77.0)	12 (20.3)	0.000
No. of not advanced (%)	94 (35.7)	47 (23.0)	47 (79.7)	
Presence of PCa (%)	105 (39.9)	77 (37.7)	28 (47.5)	0.180
Presence of clinically significant PCa (%)	72 (27.4)	51 (25.0)	21 (35.6)	0.108
<b>Prior negative biopsy</b>				
No. of patients	62	49	13	
Mean age in years (SD)	63.7 (5.81)	63.2 (5.35)	65.5 (7.25)	0.507
Mean $\mu\text{g/L}$ PSA (SD)	7.36 (1.741)	7.31 (1.738)	7.55 (1.809)	0.843
Mean mL prostate volume (SD)	54.4 (24.30)	56.9 (26.07)	45.1 (12.79)	0.221
<b>Physician</b>				
No. of advanced (%)	39 (62.9)	37 (75.5)	2 (15.4)	0.000
No. of not advanced (%)	23 (37.1)	12 (24.5)	11 (84.6)	
Presence of PCa (%)	25 (40.3)	21 (42.9)	4 (30.8)	0.430
Presence of clinically significant PCa (%)	9 (14.5)	8 (16.3)	1 (7.7)	0.432

**Table 2** Statistical analysis using logistic regression analysis

	OR	95 % CI OR
<b>All prostate cancers</b>		
Crude	0.79	0.466–1.342
Adjusted	0.79	0.411–1.504
<b>Clinically significant prostate cancers</b>		
Crude	0.69	0.387–1.234
Adjusted	0.52	0.248–1.094

means that these two variables were classified as confounders. The adjusted model regression showed no significant association between the use of Navigo<sup>TM</sup> and the detection of PCa, corrected for prostate volume and physician (OR 0.79, 95 % CI 0.411–1.504).

Identical analyses were performed for clinically significant PCa. Crude logistic regression analysis showed no significant association between the use of Navigo<sup>TM</sup> and the detection of clinically significant PCa (OR 0.69, 95 % CI 0.387–1.234). The association between the use of Navigo<sup>TM</sup> or TRUS and clinically significant PCa was not different for biopsy-naive men and men after prior negative biopsy ( $p = 0.240$ ); therefore, a sub-analysis for these two groups was also omitted. In the clinically significant PCa subgroup, the same adjusted logistic regression models were constructed, showing the same confounders as in the total group. The adjusted regression model showed no significant association between the use of Navigo<sup>TM</sup> and the detection of clinically significant PCa, corrected for prostate volume and physician (OR 0.52, 95 % CI 0.248–1.094).

## Discussion

Peltier et al. [11] published a clinical study concerning 3D TRUS prostate biopsies using the Urostation (Koelis) and concluded that CDRs improved using 3D TRUS when compared with regular 2D TRUS (50.0 vs 33.6 %, for 3D TRUS and 2D TRUS respectively). In addition, mean cancer volume detected was significantly higher using 3D TRUS.

Compared to the study of Peltier et al., in our study, there was no statistically significant difference in CDRs concerning both all PCAs and clinically significant PCAs. As patient characteristics in both studies are comparable, differences may be attributed to the use of different 3D TRUS systems or may be caused by a difference in sample sizes. We included 263 biopsy-naïve men, with 204 men in the Navigo™ group and only 59 in the 2D TRUS group, compared to 110 men in both groups in the study by Peltier et al.

In our study, there was no added value of Navigo™ system compared to conventional TRUS regarding PCA detection in biopsy-naïve men and men with prior negative biopsy. Our theory that we would be able to spread our biopsy locations better using the Navigo™ system compared to conventional TRUS does not hold regarding prostate cancer detection. However, the Navigo™ system is developed to image and record prostate biopsy cores and integrate exact locations of previous biopsy cores to plan current biopsy locations. Therefore, it would be interesting to study the value of the Navigo™ system in the active surveillance setting or in patients with ROIs on conventional TRUS for biopsy targeting. Perhaps, the benefits of 3D TRUS in more accurate targeting of ROIs can be confirmed in the latter group. This study has several limitations: first of all, retrospective design and secondly, the limited number of patients, especially in the conventional TRUS group. Moreover, the number of biopsy sessions and the ones performed by an advanced physician are statistically significant different in both groups, in favour of the Navigo™ group. The latter is a result of having only two physicians trained for the Navigo™ system, whereof one is our advanced physician. What is commonly known is that there is a learning curve for TRUS-guided biopsy. This learning curve includes 12–50 biopsy sessions, dependent on experience and biopsy quality criteria [14, 15]. As stated by Peltier, this learning curve likely also applies to 3D TRUS [11]. This is potentially disadvantageous for the Navigo group, because of less experience with 3D TRUS compared to conventional 2D TRUS. All these factors potentially created bias in our outcome measure.

However, logistic regression analyses show in all subgroups that the physician was not an independent predictor

of the outcome measure. Last, different phantom studies show better biopsy accuracy using 3D compared to 2D TRUS [6, 8, 9]. For the Navigo™ system, Cohen [12] reported a biopsy accuracy of fiducial markers of 2–3 mm. Whether a ROI is correctly sampled is therefore plausible, but not certain. Only this also applies for conventional 2D TRUS.

As described above, in the future, it would be of interest to assess the value of the Navigo™ system in a prospective, randomized study and in the active surveillance setting or in patients with ROI. Besides recording biopsy locations, from now Navigo™ is able to fuse ultrasound and mpMRI images. Targeted prostate biopsies using MR/ultrasound fusion in other platforms tend to give a higher cancer detection rate, regarding clinically significant prostate cancers [16, 17]. Therefore, a prospective study comparing MR/ultrasound-guided prostate biopsies and systematic biopsies using Navigo™ would be of interest.

## Conclusion

In our study, there is no added value of 3D TRUS using Navigo™ system compared to conventional 2D TRUS regarding PCA detection in biopsy-naïve men and men with prior negative biopsy.

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**Authors' contribution** A van der Aa was involved in data collection and manuscript writing; H. Beerlage, M. Mischi, P. Mulders, B. Schrier and H. Wijkstra was involved in protocol/project development; M. Gayet was involved in data collection and management, data analysis and manuscript writing; and P. Schmitz was involved in data collection.

**Compliance with ethical standards**

**Conflict of interest** None.

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