

1 **TOP: Prospective evaluation of a volume based, computer assisted method for**
2 **transperineal optimized prostate biopsy**

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15 **Running head:** TOP: transperineal optimized prostate biopsy

16 **Key words:** prostate biopsy, transperineal biopsy, transperineal template-guided mapping
17 biopsy, transperineal template-guided saturation biopsy, prostate cancer

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34 **Abstract**

35 Objective:

36 Prospective evaluation of a volume based, computer assisted method for transperineal
37 optimized prostate(TOP) biopsy. The TOP algorithm automates core planning for systematic
38 prostate biopsies using the 3D organ contour and an alterable volume for tumors to be
39 excluded.

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41 Subjects and methods:

42 Between 10/2013 and 03/2014 172 men underwent magnetic resonance imaging (MRI)-
43 transrectal ultrasound (TRUS) fusion biopsy with MRI targeted biopsies and systematic-TOP
44 biopsies. Systematic biopsies were placed according to TOP for detection of tumor volumes
45 greater than 0.5 ml with a minimum of 80% organ coverage in prostates up to 50 ml (70% in
46 larger organs).

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48 Results:

49 Median 24 TOP cores and 3 MRI-targeted biopsies (TB) have been placed. Prostate cancer
50 (PCa) was detected in 112 of 172(65%) of men. TOP detected 109(97%) and TB 62(55%).
51 Significant cancer (Gleason score ≥ 7) was detected in 75(44%) of men and of these TOP
52 detected 73/75(97%) and TB 51/75(68%). Overall, systematic-TOP sampling significantly
53 outperformed TB for the detection of both, all PCa as well as significant PCa ($p < 0.0001$,
54 $p = 0.0005$).

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56 Conclusion:

57 The TOP method is innovative by integrating the individual prostate volume and PCa-volume
58 detection thresholds. In the present cohort, it diagnosed more significant tumors than TB
59 alone. However, at the same time more low-risk tumors are detected.

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62 **Introduction:**

63 The goal of prostate cancer (PCa) diagnosis is detection of significant tumors and accurate
64 characterization of disease in order to reliably stratify patients for an appropriate treatment
65 option such as active surveillance, focal therapy or radical treatment with prostatectomy or
66 radiation. Conventional 12 core trans-rectal ultrasound (TRUS)-biopsy shows an average
67 sensitivity of 48% for detecting clinically significant PCa [1] and is therefore clearly not
68 fulfilling those demands. Multiparametric magnetic resonance imaging (mpMRI) in
69 combination with fusion-biopsy might overcome this insufficiency. The MRI targeted
70 approach alone was shown to diagnose 10-30% more significant cancers and 10-17% less
71 indolent tumors [2,3] in comparison with 12 core standard TRUS-biopsy. Nevertheless,
72 mpMRI has been shown to miss significant cancers in 10-16% [4–6] as well. In combination
73 with targeting errors of mpMRI-fusion techniques this can add up to 22-36% [5,6] of
74 significant tumors being missed, illustrating that for the time being systematic biopsies
75 should not be omitted . There is not yet consensus on what might be the ideal approach and
76 amount of systematic biopsies as this is always a challenging compromise between maximal
77 diagnostic accuracy, potential side effects, cost and practicability. Increasing the sampling
78 density of conventional transrectal biopsy showed practically no increased PCa detection
79 rate compared to standard 12 core TRUS biopsy [7], most probably due to difficulties
80 sampling the anterior and apical regions using the transrectal approach [8,9]. The
81 transperineal approach as alternative allows systematic core placing in the whole prostate
82 including apex, anterior and transition zones [10, 11]. Reproducible high sensitivity has been
83 reported using transperineal template mapping biopsy (TTMB) which requires an extensive
84 amount of median 48 cores per patient [12,13], whereas a prostate volume adapted
85 saturation approach of 24 to 38 cores has been suggested by the Ginsburg study Group [14].

86

87 In the present study we investigate a novel volume based, automated core-placement
88 method for transperineal optimized prostate (TOP) biopsy, which can be used in addition to
89 fusion biopsies and also in patients without suspicious MRI-findings or MRI incompatibility.

90

91 **Patients and methods:**

92 Study Population:

93 Between October 2013 and March 2014 a total of 172 men with abnormal PSA or suspicious
94 digital-rectal examination (DRE), persistent suspicion of prostate cancer after previous
95 negative biopsy or under active surveillance underwent targeted MRI/TRUS-fusion biopsy
96 (TB) and systematic-TOP biopsy. Institutional review board approval was granted (S-
97 280/2012) and informed consent was obtained from all patients before each intervention.
98 Data are reported according to START (Standards of Reporting for MRI-targeted biopsy
99 studies) criteria [15] (Table 1).

100

101 Imaging:

102 mpMRI was performed using a 3T system without endorectal coil (Magnetom, Siemens,
103 Erlangen, Germany) as described previously [5] (Supplementary Table 1). MRI analysis was
104 performed prospectively by, or under supervision of an expert urologist (HPS)
105 according to the 2012 European Society of Urogenital Radiology guidelines [16]. Reflecting
106 clinical routine at the time of data collection, analysis was performed based on PIRADS
107 Version 1 [16] and radiologists were not blinded to clinical data.

108

109 Model of Systematic Random Sampling:

110 MRI/TRUS-fusion biopsies were performed using the transperineal, template-guided
111 BiopSee® System (MedCom, Darmstadt, Germany). This system consists of a computer, a
112 biplane endorectal ultrasound (US) device fixed to a stepper, a template likewise attached to
113 the stepper and electronics to control ultrasound position and orientation. During
114 intervention a 3-dimensional (3D) US is acquired by moving the device with the stepper
115 along the prostate from cranial to caudal. Next, 3D US and MRI are fused together in a semi-
116 automated manner. In general, a rigid fusion algorithm is applied. However, if needed, the
117 3D US can be contoured as well with subsequent elastic fusion of US and MRI imaging data.
118 Afterwards biopsy cores are placed virtually within the 3D data set. Biopsies are then taken
119 through the software-suggested template hole under continuous longitudinal US guidance
120 [17]. The system can be operated using the novel TOP algorithm for computer-aided,
121 automated core planning for systematic prostate biopsies using the 3D organ contour and an
122 adjustable volume for tumors to be detected (*vd*), which can be selected freely by the

123 urologist. Thereby the requested number of cores (N) is calculated with $N = CA_{DR} \times P_{eff} / bc$
124 with P_{eff} being the prostate volume to be sampled (approximated as $P_{eff} = \pi/6 \times (a-d/2) \times (b-$
125 $d/2) \times (c-d/2)$ with a , b and c being the prostate dimensions in apical-basal, left-right and
126 ventral-dorsal directions and d being the approximated diameter of the disease lesion), bc
127 being the core sampling volume (based on vd and an estimated core length of 1.7 to 2 cm)
128 and CA_{DR} being the volitional cancer detection rate which can be equated with the achieved
129 organ coverage. Cores are equally and automatically distributed over the complete organ
130 volume (Figure 1).

131

132 Core placement and TOP characteristics applied in this study:

133 After segmentation of the prostate on MRI with marking the prostate contour and suspicious
134 lesion and MRI/TRUS-fusion, automatic placement of systematic biopsies was performed
135 using a vd of 0.5 ml. This means that the virtual core placing is performed with a needle
136 distribution sampling each conceivable tumor lesion ≥ 0.5 ml in the complete prostate
137 (100%). Yet, reflecting clinical routine, the operator was able to remove or change core
138 positions if wanted, for example cores crossing the urethra. However, we required a minimal
139 organ coverage of 80% for a prostate volume ≤ 50 ml and 70% for a prostate volume > 50 ml
140 in order to be included in this study. TB were placed manually on mpMRI suspicious lesions
141 PIRADS > 2 , independently of the location of TOP cores with a median amount of 2 cores per
142 lesion. Subsequently, biopsies were performed starting with TB and followed by systematic-
143 TOP sampling.

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145 Histopathologic analysis:

146 Histopathologic biopsy specimens were analyzed under the supervision of a dedicated
147 uropathologist (KW), according to the International Society of Urological Pathology
148 standards [18]. Significant PCa was defined as Gleason score ≥ 7 .

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150 Statistical Analysis:

151 Statistical analysis was performed using SPSS Statistics (V23, IBM Corp, Armonk, NY, USA). P
152 values were calculated using McNemar test with a significance level of 5%. To evaluate the
153 magnitude of differences in the detection rates of systematic-TOP and TB rate differences
154 along with 95% confidence intervals were calculated according to Tango [19].

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165 **Results:**

166 The 172 men included in this study had a median age of 65 years and pre-biopsy PSA of 7.2
167 ng/ml. For 95 men this was their primary biopsy, 77 men already had a previous TRUS
168 biopsy. 51 of them underwent repeat-examination due to persistent suspicion of cancer
169 after previous negative TRUS biopsy and 26 for re-stratification purposes with assumed low-
170 risk disease amenable for active surveillance. The median amount of systematic-TOP
171 biopsies per patient was 24. Table 1 summarizes the characteristics of the study population.
172 PCa was diagnosed in 112 men (65%) and clinically significant disease was identified in 75
173 men (44%). Subgroup analysis showed an overall cancer detection rate of 72% (significant
174 disease 54%) for the primary-biopsy cohort, 45% (significant disease 24%) for the repeat-
175 biopsy cohort and 81% (significant disease 46%) for the active surveillance-cohort. The
176 pathological features stratified to Gleason scores and PIRADS are summarized in Table 2. The
177 comparison of systematic-TOP and TB (Table 3) demonstrates clear inferiority of TB for both,
178 all PCa and significant PCa ($p < 0.0001$ and $p = 0.0005$) with TB missing 30 of 92 PCa and 19 of
179 70 significant PCa in case of PIRADS > 2 lesions. Notably, in 12 cases of the 30 PCa missed by
180 TB and detected by the systematic approach, the positive TOP cores were located in the
181 prostate region with the MRI-suspicious lesion, clearly demonstrating a targeting error of the
182 TB approach. Systematic-TOP did miss cancer as well. However, taking the combined
183 approach as reference (Table 3), no significant inferiority was revealed for all PCa and
184 significant PCa, respectively ($p = 0.2482$ and $p = 0.4795$). Altogether, in a total number of 112
185 PCa locations, systematic TOP detected 109 and missed 3, of whom 2 were classified as
186 significant PCa. Retrospective analysis of these 3 cases identified operator error in one case,
187 in a second case a true error (a low-risk tumor found with TB was missed by systematic-TOP
188 cores), and the third case could not be clearly assigned to one or the other error class.

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191 **Discussion:**

192 The here introduced systematic-TOP prostate biopsies have two major advantages. First, the
193 possibility to adjust the volume for tumors to-be-detected (*vd*) and the volitional cancer
194 detection rate thereby allowing an approach adaptable to each individual patient's needs
195 and risk assessment. Second, it is to the greatest possible extent independent from the
196 operator and is therefore an ideal tool to assist untrained urologists as well as for creating
197 intra-and inter-observer independent examinations.

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199 The TOP algorithm uses the organ volume, the desired percentage of organ coverage and
200 the adjustable *vd* volume for calculating the number of cores needed; coverage and *vd* are
201 freely adjustable. By using a *vd* of 0.5 ml and a minimal organ coverage of 80% for a prostate
202 volume ≤ 50 ml and of 70% for a prostate volume > 50 ml, systematic-TOP with a median
203 amount of 24 cores per patient significantly outperformed TB. Using such a volume adjusted
204 stringent systematic saturation approach, the combination of the two biopsy methods did
205 not have significant additional benefit. The detected overall-cancer rates with 65% for all
206 patients and 72%, 45% and 81% for the primary biopsy cohort, the repeat biopsy cohort and
207 the surveillance-cohort, respectively, are clearly compatible compared to other
208 transperineal template-guided saturation (TTSB) or mapping biopsy studies (TTPM): for
209 primary biopsy cohorts detection rates of 54%-76% have been reported using a mean
210 amount of 19-54 cores [20–23], for repeat biopsy cohorts detection rates of 26%-68% with a
211 mean amount of 18-59 cores have been reported [21,22,24–28]. In series in which TTPM
212 biopsies was followed by RP, TTPM was highly accurate in detecting and excluding clinically
213 significant disease [30,31]. This seems plausible as the TTPM approach can technically miss
214 only those tumors that are smaller than the distance between the adjacent cores (5-mm).
215 Our approach using an adjustable *vd* follows the same principle, since comparably to TTPM
216 also only those tumors that are smaller as the *vd* can be missed. On the other side, it is more
217 flexible because the *vd* can be changed in 0.1ml steps.

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219 The ideal amount and spatial distribution in the different prostate zones, or alternatively the
220 location-specific ideal core density, needs yet to be investigated. Only a little amount of
221 studies directly compares different approaches. In a computer-simulated study of
222 transperineal prostate biopsy Crawford et al. compared biopsies using grid sizes of 5-mm

223 (method A) and 10-mm (method B) and found a significant difference between the detection
224 rates for all (84% vs. 59%) and for significant PCa (95% vs 78%) [12]. Valerio et al. examined
225 the value of three artificially simulated modified strategies comparing them against full 5-
226 mm TTPM. Strategy 1 excluded the anterior areas of the prostate; strategies 2 and 3
227 involved a reduced sampling density from 5 to 10 mm by omitting intervening areas. For
228 detection of clinically significant disease the strategies 1, 2 and 3 had sensitivities of 78%,
229 85% and 84%, respectively. Contrary to that a study conducted at Nara Medical University
230 examined the cancer detection rates at 5 mm, 10 mm and 15 mm core intervals and did not
231 find any significant difference between the 5 mm and 10 mm intervals (personal
232 communication).

233

234 A drawback of all, TTPM, TTSB and the here introduced systematic-TOP strategy, is the
235 necessity for general anesthesia as well as the larger number of needles, resulting in
236 corresponding larger trauma, extensive pathological processing and associated cost.
237 Nevertheless, as described in the introduction, transperineal systematic biopsies cannot yet
238 be safely omitted in favor of a TB only approach. Moreover, they are well tolerated and have
239 only minor, temporarily side effects like haematuria, short term catheterization, erectile
240 deterioration or fever with no septic complications being reported [32]. Thus, patients seem
241 to handle them at least as good as conventional TRUS biopsy [33]. Our data supports the
242 hypothesis that next to MRI invisible tumors one main reason for negative TB are targeting
243 errors [34]. Thus, improving TB targeting or, alternatively, implementing target saturation of
244 suspicious MRI locations, might be a way to reduce systematic biopsies in the future.

245

246 A limitation of our study is the missing direct comparison to a standardized reference test
247 such as conventional biopsy or radical prostatectomy. Also, reflecting clinical routine at our
248 institution at the time of the study, the operator was not blinded to MRI results and
249 systematic-TOP and TB were performed by the same operator. Data collection was
250 performed prospectively, but analysis was performed retrospectively. We defined significant
251 disease as Gleason score ≥ 7 , which is debatable. However, a standard definition of
252 significant disease for TTSB, TTPM and fusion-biopsy is still missing. Various definitions are
253 used throughout the literature, which has to be kept in mind when comparing different
254 studies.

255 **Conclusion:**

256 The TOP method is innovative by integrating the individual prostate volume and detection
257 thresholds. With a volume for tumors to be detected of 0.5 ml, TOP diagnosed significantly
258 **more** significant tumors than targeted biopsies. However, at the same time more low-risk
259 tumors are detected.

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414

415 **Conflict of interest:**

416 G Sakas is CEO of MedCom. P Zogal is an employee of MedCom. The other authors have no
417 conflicts of interest to disclose.

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444 **Tables:**

445 **Table 1.** Study population and results according to START criteria.

Men included in analysis, n	172
Age, years, median (IQR)	65 (58 – 71)
Pre-biopsy PSA level, ng/ml, median (IQR)	7.2 (5.4 – 10.2)
Suspicious DRE findings (≥ T2), n (%)	37 (21.5)
Prostate volume, ml, median (IQR)	46 (36 – 60)
PSA density, median (IQR)	0.15 (0.10 – 0.26)
Men without prior prostate biopsy, n (%)	95 (55.2)
Men with prior prostate biopsy, n (%)	77 (44.8)
Number of cores in prior biopsy, median (IQR)	12 (10-17)
Patients undergoing active surveillance, n (%)	26 (15.1)
Men with PI-RADS > 2 lesions on mpMRI, n (%)	127 (73.8)
Number of lesions PI-RADS > 2	167
Patients with one PI-RADS > 2 lesion	90
Patients with two PI-RADS > 2 lesion	34
Patients with three PI-RADS > 2 lesion	3
Overall PI-RADS score 3 lesions, n (% of PI-RADS > 2)	75 (44.9)
Overall PI-RADS score 4 lesions, n (% of PI-RADS > 2)	53 (31.7)
Overall PI-RADS score 5 lesions, n (% of PI-RADS > 2)	39 (23.4)
Biopsies per patient, median (IQR)	27 (25 – 29)
Systematic-TOP biopsies per patient, median (IQR)	24 (23 – 27)
Targeted biopsies per patient and per lesion, median (IQR)	3 (0 – 4), 2 (2 – 3)
Organ coverage with biopsies, median (IQR)	90 (84 – 93)

START = Standards of Reporting for MRI-targeted Biopsy Studies, n = Number, IQR = interquartile range, PSA = prostate-specific antigen, DRE = digital rectal examination, mpMRI = multiparametric magnetic resonance imaging, PI-RADS = Prostate Imaging Reporting and Data System, TOP= transperineal optimized prostate.

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447 **Table 2.** Cancer detection rates according to PIRADS.

PIRADS	All (%)	≤2 (%)	3 (%)	4 (%)	5 (%)
No PCa	60 (35)	25 (15)	21 (12)	13 (8)	1 (1)
GS 3+3	37 (22)	15 (9)	14 (8)	7 (4)	1 (1)
GS 3+4	52 (30)	4 (2)	14 (8)	21 (12)	13 (8)
GS 4+3	11 (6)	1 (1)	2 (1)	0 (0)	8 (5)
GS 4+4	3 (2)	0 (0)	0 (0)	0 (0)	3 (2)
GS 4+5/5+4	9 (5)	0 (0)	0 (0)	1 (1)	8 (5)

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449 PCa = Prostate cancer, GS = Gleason Score

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457 **Table 3.** Comparison of systematic-TOP and targeted biopsies in patients with PIRADS > 2
 458 lesions.

All tumors	Detection rate in systematic-TOP biopsy	89	} Mc Nemar Test: p < 0.0001 Paired difference ^a (CI): 21.3% (13.5%-29.8%)
	Detection rate in targeted Biopsy	62	
	Combined detection rate	92	
Significant tumors (GS ≥ 3+4)	Detection rate in systematic-TOP biopsy	68	} Mc Nemar Test: p = 0.0005 Paired difference ^a (CI): 13.4% (7.1%-20.9%)
	Detection rate in targeted Biopsy	51	
	Combined detection rate	70	
		459	
^a according to Tango GS = Gleason score, CI = confidence interval		460	

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462 **Figure legends:**

463 **Figure 1.** **A** Needle plan following systematic-TOP recommendations. **B and C** Moving the
 464 biopsy needle along the path. **D** Scheme of the prostate volume covered by one biopsy core.

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466 **Figure 2.** Patient with a PIRADS 5 lesion undergoing MRI-fusion TB and systematic-TOP
 467 biopsies. **A** Axial scheme of the core distribution with 22 systematic-TOP cores and 4 TB
 468 cores. **B** core distribution on axial ultrasound view. **C** Core distribution on 3-dimensional
 469 prostate reconstruction. **D** Sagittal core distribution. **Blue arrow** The button “Automatic
 470 placement” activates the systematic-TOP placement of cores. **Orange arrow** Selection of the
 471 tumor volume to be detected. **Green arrow** TOP statistics providing amongst others organ
 472 coverage (93%) and theoretical needle count (22).

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489 **Supplementary Tables:**

490 **Supplementary Table 1.** Multiparametric MRI protocol including sequence parameters.

Parameter	T1 TSE	T2 TSE	epi-2D	DCE TWIST
TR ms/ TE ms	792/11	5120/143		3100/52 4.42/2.2
Flip angle (°)	90	90		90 15
ETL length/ Epi- factor	72	12		96 x
Averages	2	4		5 x
b-value	x	x	0, 50, 100, 150, 200, 250, 800, 1000	x
Section thickness (mm)	5	3		3 1,5
FOV (mm)	320	300		280 400
Resolution	1.1 x 1.0	0.8 x 0.7		2.2 x 2.2 1.6 x 1.6
Acquisition time (min)	03:51	04:14		05:04 05:18

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TR- Repetition Time, TE- Echo Time, ETL- Echo Train Length, FOV- Field of View, epi- Echo Planar Imaging, TSE- Turbo Spin Echo, TWIST- Time-resolved angiography With Interleaved Stochastic Trajectories, SE- Spin Echo, DCE- Dynamic contrast enhancement

Figure 1.

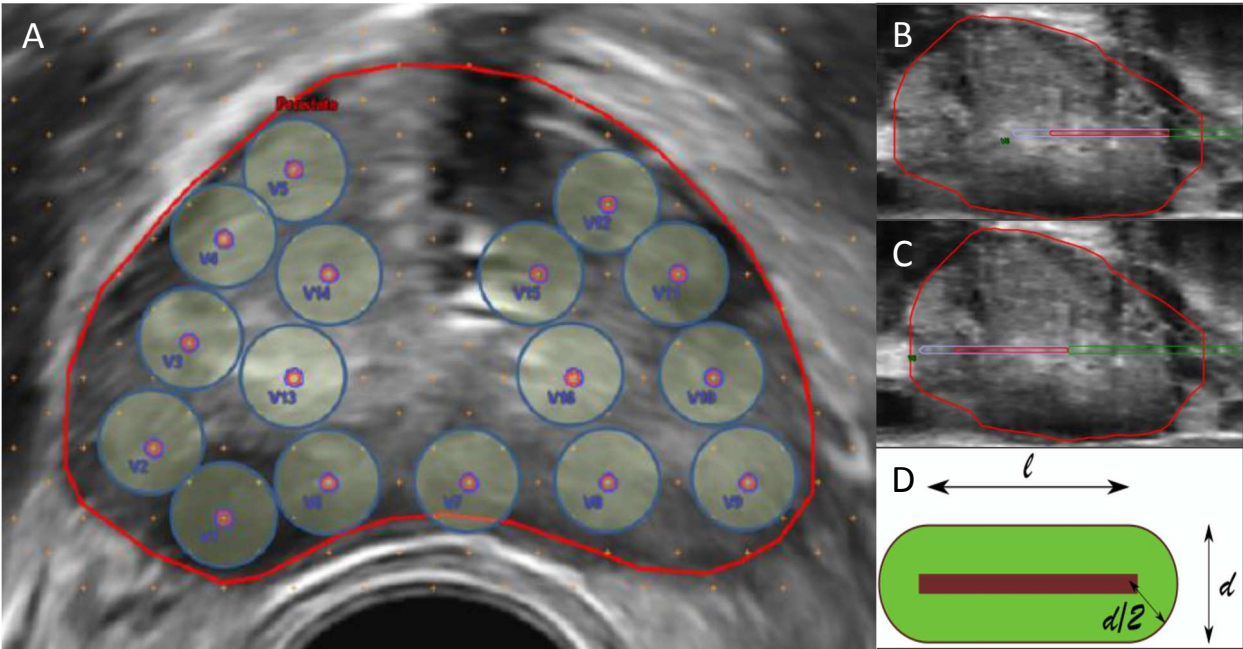


Figure 2.

