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## Platinum Priority – Prostate Cancer

Editorial by Michael W. Kattan and J. Stephen Jones on pp. 9–10 of this issue

# Biopsy Schemes with the Fewest Cores for Detecting 95% of the Prostate Cancers Detected by a 24-Core Biopsy

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### Article info

#### Article history:

Accepted August 11, 2009

Published online ahead of print on August 19, 2009

#### Keywords:

Prostatic neoplasms  
Prostate biopsy  
Diagnosis transrectal ultrasound



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### Abstract

**Background:** The most efficient number and location of prostate biopsies remains a matter of debate.

**Objective:** To identify the combination (number and location) of sampling sites that permits the detection of 95% of the prostate cancers (PCa) detected by a 24-core biopsy (24PBx).

**Design, setting, and participants:** Six hundred and seventeen consecutive patients with a suspicion of PCa were prospectively enrolled.

**Intervention:** A transrectal ultrasound-guided systematic 24PBx was prospectively performed with local anesthesia in an outpatient setting. The 24PBx was obtained by the overlapping of medial sextant, lateral sextant, octant subcapsular, and quadrant transition cores. Before fixation, each single core was individually marked and inked according to the prostatic location sampled.

**Measurements:** We relied on a classification and regression tree analysis to identify four subgroups of patients with different PCa detection risk at initial biopsy, according to their clinical characteristics. Subsequently, we set the cancer-positive rate of the 24PBx at 100% and calculated PCa detection rates for 255 possible combinations of sampling sites. We selected the most advantageous biopsy scheme (defined as the combination of sampling sites that detected 95% of all the cancers with the minimal number of biopsy cores) for each patient subgroup. Finally, we internally validated the tumor detection rates by using the 10-fold cross-validation method.

**Results and limitations:** The 24PBx detected PCa in 289 patients (46.8%). The analysis revealed that the most advantageous schemes for patients with a negative digital rectal exam (DRE), prostate volume (PV)  $\leq 60$  cm<sup>3</sup>, and age  $\leq 65$  yr was a combination of a 16-core biopsy. For patients with a negative DRE, PV  $\leq 60$  cm<sup>3</sup>, and age  $> 65$  yr or a negative DRE and PV  $> 60$  cm<sup>3</sup>, the most advantageous scheme was two different combinations of a 14-core biopsy. Finally, the sampling that permits detection of 95% of cancers in patients with a positive DRE was a combination of a 10-core biopsy.

**Conclusions:** The most beneficial scheme varied according to the clinical characteristics of the patients. We propose a user-friendly flowchart to identify the most advantageous set of sampling sites according to patients' characteristics.

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## 1. Introduction

Since the introduction of the systematic sextant biopsy protocol by Hodge, several groups have demonstrated that standard sextant prostate biopsies significantly underestimate cancer and have proposed more extensive biopsy schemes involving 10–18 cores [1]. It has been demonstrated that the far lateral aspect of the peripheral zone of the prostate is crucial to optimize the detection rate. Laterally directed biopsies, which also aim at sampling the lateral horn of the prostate, yield about a 25% increased ability to detect prostate cancer (PCa) [1–3]. The apex and the base of the peripheral gland are the sites where PCa is most likely to be located and where the biopsies should be directed, whereas midline biopsies have the lowest probability of being positive [1–6].

The most efficient number and location of prostate biopsies remain a matter of debate. It is not clear whether it is always necessary to rely on the same protocol or to modify it according to the different clinical parameters, such as prostate-specific antigen (PSA) value, digital rectal examination (DRE) findings, or prostate volume (PV). Moreover, it is still controversial whether the detection rate may vary simply with additional biopsies or be due to the different locations from which the cores are taken.

We evaluated cancer detection rates on an individual core basis after a 24-core prostate biopsy (24PBx) and investigated the ability of various biopsy regimens, which are characterized by the number and anatomic location of cores taken, to detect PCa. We also attempted to identify the most advantageous number and location of the cores to detect the maximum number of PCa with the minimum number of cores, according to different clinical parameters.

## 2. Patients and methods

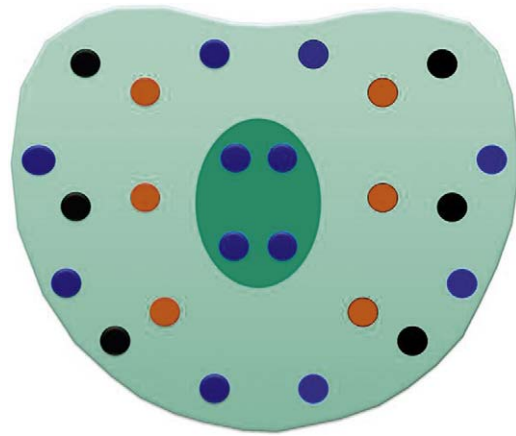
### 2.1. Procedure

Following institutional review board approval, from September 2005 to June 2008 we prospectively performed a saturation biopsy in 617 consecutive patients suspected of harboring PCa. The indications to perform an initial biopsy were PSA between 2.5 and 4.0 ng/ml plus abnormal DRE and/or transrectal ultrasound (TRUS) findings or PSA  $\geq 4$  ng/ml regardless of DRE and TRUS findings. Five dedicated urologists performed the procedures during this period. Patients were given a fluoroquinolone antibiotic on the day of the procedure and for 4 d subsequently. Patients were prescribed enemas 1 d and 3 h before the procedure.

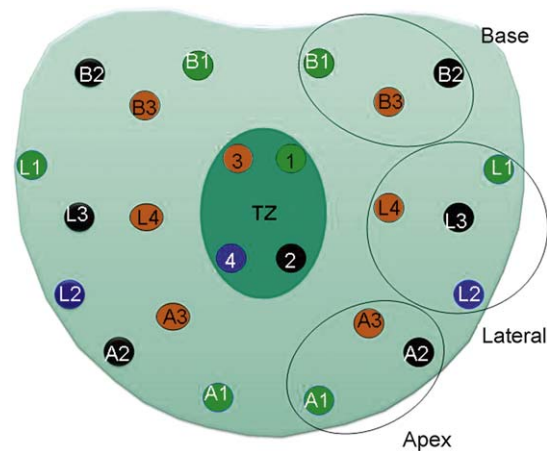
Each physician used a TRUS end-fire probe at a variable frequency of 5–7.5 MHz (Hitachi side-fire probe on a Hitachi Esaote 560 or H21 machine; Hitachi Medical Headquarters, Tokyo, Japan) to guide the 18-gauge transrectal needle for prostate biopsy.

Saturation biopsy was done on an outpatient basis using topical prilocaine-lidocaine cream combined with peripheral nerve block that included the endorectal injection of 5 ml lidocaine (2%) bilaterally as we have previously described [7].

Biopsies were performed using 18-gauge needles and a biopsy gun, providing 15-mm-long tissue cores. The biopsy patterns targeted six sectors (apex, lateral, and base, bilaterally) and the transition zone to ensure a broad sampling area (Figs. 1 and 2). Three or four cores were taken from a specific zone of the sector for a total of 24 cores, and each



**Fig. 1** – The figure shows the exact position of the 24 cores. The orange cores belong to the classic Hodge scheme, the black cores to the Stamey scheme, and the blue cores to the more lateral and subcapsular cores.



**Fig. 2** – The number on the core represents the exact sequence and order of how the cores were taken and put in the sponge tissue on the sandwich cassette. The figure also shows the three sectors (apex, lateral, and base) and the transition zone from which the cores were taken and the colors used to mark each single core on the cassette. We started from the right lobe to the left lobe, from the apex to the base. A = apex; L = lateral; B = base.

single core was individually marked. As shown in Fig. 1, the scheme consisted of the overlapping of the classical sextant scheme of Hodge (orange points), the more lateral sextant scheme of Stamey (black points), eight more lateral and subcapsular cores (blue points), and four cores from the transition zone. Fig. 2 shows the exact sequence of cores that was taken, starting from the apex (A1, A2, A3), lateral (L1, L2, L3, L4), and base (B1, B2, B3) of the right lobe, and base, lateral, and apex of the left lobe, and, at the end, the four cores of the transition zone (posterior left, anterior left, posterior right, and anterior right). The 24 cores were immediately put on sponge tissue in seven different sandwich cassettes and individually inked (Fig. 2) with different colors to mark the site from which they were collected [8]. The cassettes were soaked in a glass full of Bouin solution for 1 s to fix the colors and then preserved in a pot with 10% formalin. All slides were reviewed by a single experienced uropathologist (MF) using contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), lesion suspicious but not diagnostic for adenocarcinoma (atypical small acinar proliferation of prostate [ASAP]), and PCa. All complications were recorded in our database.

## 2.2. Statistical analysis

One-way analysis of variance and  $\chi^2$  analyses were used to compare means and proportions, respectively. Because the sextant scheme of Stamey provided the highest detection rate with six cores, we chose this approach as a baseline. Therefore, we added one single core per each side of the prostate, and we calculated the cancer detection rates for each scheme with 8, 10, 12, 14, 16, 18, 20, and 24 cores (considering all the biopsies of the transitional zone taken together). A total of 255 possible combinations were created, according to the sites of the cores. Patients with a HGPIN or ASAP were considered negative cases. Because the exact prevalence of cancer cannot be assessed, to define how many cancers were detected with the different schemes (number and sites), we assumed that virtually all PCa was detected by the 24PBx. Consequently, we set the cancer-positive rate of the 24PBx at 100%, and we calculated the percentage of cancer detected by every scheme in all the possible combinations. Recursive partitioning analysis was used to evaluate all possible combinations of sampling sites and then to choose a combination providing the highest cancer detection rate at a given number of cores [9,10]. We selected the most advantageous combination of sampling sites that detected >95% of the cancer detected with the minimum number of cores.

Because patients with different baseline characteristics have dissimilar PCa detection rates, we decided to identify subgroups of patients according to the risk of having PCa at initial biopsy and to repeat all the analyses in each subgroup. To split the population, we relied on a classification and regression tree analysis where all the available clinical variables (PSA, DRE, age, and PV) were included in tree modeling to predict the presence of tumor at initial biopsy. The computer-based modeling automatically proceeded to the selection and categorization of the variables included. The overall population was automatically split in four subgroups with different PCa detection risks: (1) DRE negative, PV  $\leq 60$  cm<sup>3</sup>, and age  $\leq 65$  yr; (2) DRE negative, PV  $\leq 60$  cm<sup>3</sup>, and age  $> 65$  yr; (3) DRE negative and PV  $> 60$  cm<sup>3</sup>; and (4) DRE positive. A single patient does not fit in multiple risk groups. Subsequently, we repeated all the analyses in the four subgroups of patients. Finally, to generalize our results, which might be biased by overfitting, we decided to validate the tumor detection rates by using the 10-fold cross-validation method. The significance level for all tests was set at 0.05. All statistical analyses were performed using SPSS 11.0 software (SPSS, Chicago, IL, USA).

## 3. Results

All patients tolerated the biopsies well, and the planned numbers of cores were always obtained. Table 1 shows the characteristics of the patients. Cancer was detected in 289 men (46.8%). At a given number of cores, the cancer detection rates varied significantly according to the different combination of sites considered (Table 2). The cross-validated mean cancer detection rates increased significantly with the increasing number of cores. The following mean cancer detection rates (95% confidence interval) were found for all of the 255 possible combinations and 24 cores: 8 cores, 36.3% (35.4–37.3%); 10 cores, 38.7% (38.2–39.2%); 12 cores, 40.6% (40.3–40.9%); 14 cores, 42.2% (41.9–42.4%); 16 cores, 43.5% (43.3–43.8%); 18 cores, 44.6% (44.3–44.9%); 20 cores, 45.6% (45.1–46.0%); and 24 cores, 46.8%. Only the mean cancer detection rates of the 12-core scheme were significantly different from those of the 24-core scheme ( $p = 0.047$ ), whereas the mean cancer detection rates of the 14-core scheme were not statistically higher than those of the 24-core scheme ( $p = 0.156$ ). Fig. 3

**Table 1 – Patient characteristics of the study population\***

Parameter	Initial 24-core PBx (n = 617)
Age, yr	65.4 $\pm$ 8.0
PSA (ng/ml)	9.0 $\pm$ 22.2
• PSA $\leq 4.0$ ng/ml	148 (24%)
• PSA 4.1–10 ng/ml	295 (48%)
• PSA $> 10.1$ ng/ml	174 (28%)
Free PSA, %	0.18 $\pm$ 0.08
Prostate volume, cm <sup>3</sup>	66.6 $\pm$ 36
Transitional zone volume, cm <sup>3</sup>	39.9 $\pm$ 30
PSA density	0.13 $\pm$ 0.10
PSA density transitional zone	0.30 $\pm$ 0.50
Abnormal DRE findings	19%
PCa	46.8%
HGPIN	8.9%
ASAP	1.13%
HGPIN and ASAP	0.8%

ASAP = atypical small acinar proliferation of prostate; DRE = digital rectal examination; HGPIN = high-grade prostatic intraepithelial neoplasia; PBx = prostate biopsy; PCa = prostate cancer; PSA = prostate-specific antigen.  
\* Data are presented as mean plus or minus standard deviation.

shows the cross-validated mean percentages of cancer detected according to the number of cores at initial biopsy. The variability of the mean percentage of cancer detected by the schemes significantly decreased with an increasing number of cores (Fig. 3). Moreover, the variability was significantly higher in patients with a negative DRE than in those with a positive DRE ( $p = 0.001$ ), in patients with a PSA  $< 10$  ng/ml than in those with a PSA  $> 10$  ng/ml ( $p = 0.005$ ), and in patients with a PV  $> 60$  cm<sup>3</sup> than in those with a volume  $< 60$  cm<sup>3</sup> ( $p = 0.04$ ; Fig. 4). Fig. 5 shows the different site-specific cancer-positive rates.

Subsequently, we determined the best combination of sampling sites that detected >95% of the cancers with the minimum number of biopsy cores, according to the clinical characteristics of the patients. As shown in Fig. 6, we identified four different PCa risk groups: (1) DRE negative, PV  $\leq 60$  cm<sup>3</sup>, and age  $\leq 65$  yr; (2) DRE negative, PV  $\leq 60$  cm<sup>3</sup>, and age  $> 65$  yr; (3) DRE negative and PV  $> 60$  cm<sup>3</sup>; and (4) DRE positive, and we provided the most advantageous sampling scheme for each patient category.

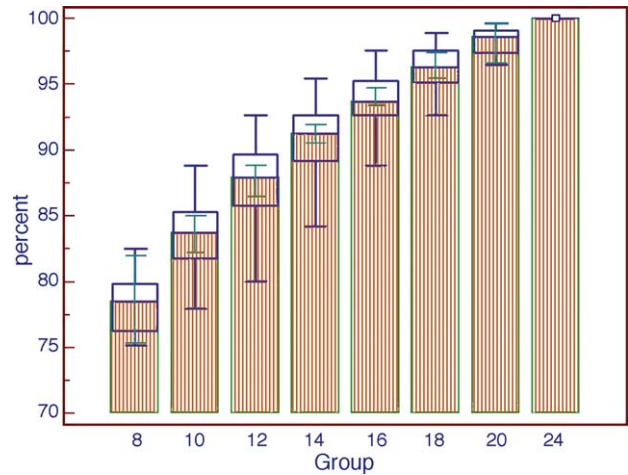
As shown in Fig. 6, the provided flowchart allows clinicians to choose the most advantageous schemes according to the clinical characteristics of the patients. The analysis revealed that the most advantageous scheme for patients with a negative DRE, PV  $\leq 60$  cm<sup>3</sup>, and age  $\leq 65$  yr was a combination of a 16-core biopsy. For patients with a negative DRE, PV  $\leq 60$  cm<sup>3</sup>, and age  $> 65$  yr or a negative DRE and PV  $> 60$  cm<sup>3</sup>, the most advantageous scheme was two different combinations of a 14-core biopsy. Finally, the sampling that allows the detection of 95% of cancers in patients with a positive DRE was a combination of a 10-core biopsy (Fig. 6). Fig. 7A–D shows the core's location according to the proposed schemes.

Macroscopic hematuria for  $> 3$  d occurred in 74% of patients and lasted an average of 4.5 d. Hematospermia was common and lasted 3–4 wk. Rectal bleeding was reported to be present only for 1 d and occurred in 3.2% of patients.

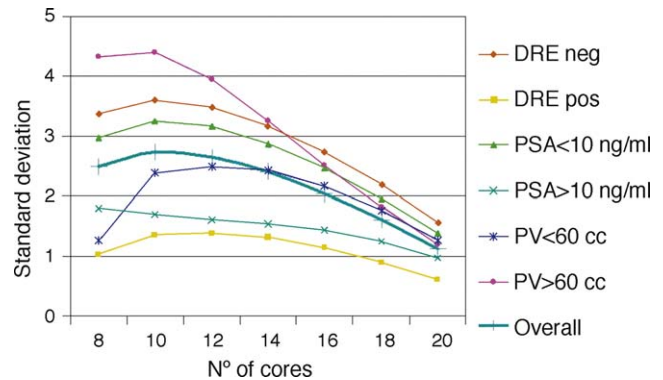
**Table 2 – Percentage of cancers detected (95% CI) at initial biopsy according to different clinical parameters and number and location of cores**

No. of cores	DRE positive	DRE negative	PSA <10 ng/ml	PSA >10 ng/ml	PV ≤60 cm <sup>3</sup>	PV >60 cm <sup>3</sup>
8	95.0 ± 1.0 (94.1–95.8)	72.6 ± 3.3 (69.7–75.4)	75.8 ± 2.9 (73.3–78.3)	88.8 ± 1.8 (87.3–90.3)	79.2 ± 1.9 (77.6–80.8)	76.4 ± 4.3 (72.8–80.0)
10	96.0 ± 1.3 (95.5–96.6)	79.1 ± 3.6 (77.7–80.5)	81.5 ± 3.2 (80.3–82.8)	91.4 ± 1.7 (90.7–92.0)	84.0 ± 2.3 (83.0–84.9)	82.2 ± 4.4 (80.5–83.9)
12	96.0 ± 1.3 (96.5–97.3)	84.4 ± 3.4 (83.5–85.4)	86.1 ± 3.1 (85.3–87.0)	93.4 ± 1.6 (93.0–93.9)	87.8 ± 2.5 (87.1–88.5)	86.9 ± 3.9 (85.8–88.0)
14	97.0 ± 1.3 (97.4–98.0)	88.8 ± 3.1 (88.1–89.6)	89.9 ± 2.8 (89.3–90.6)	95.1 ± 1.5 (94.8–95.5)	91.0 ± 2.4 (90.5–91.6)	90.7 ± 3.2 (90.0–91.5)
16	98.4 ± 1.1 (98.1–98.7)	95.4 ± 2.7 (91.7–93.2)	93.1 ± 2.4 (92.5–93.8)	96.6 ± 1.4 (96.3–97.0)	93.8 ± 2.1 (93.2–94.4)	93.9 ± 2.5 (93.2–94.5)
18	99.0 ± 0.9 (98.6–99.3)	95.4 ± 2.1 (94.6–96.3)	95.8 ± 1.9 (95.0–96.6)	97.9 ± 1.2 (97.5–98.4)	96.1 ± 1.7 (95.5–96.8)	96.4 ± 1.8 (95.7–97.1)
20	99.5 ± 0.6 (99.0–100)	97.9 ± 1.5 (96.6–99.2)	98.1 ± 1.3 (96.9–99.2)	99.0 ± 0.9 (98.2–99.9)	98.2 ± 1.2 (97.1–99.2)	98.4 ± 1.2 (97.4–99.4)
24	100	100	100	100	100	100
24 cores different from p < 0.05	<10	<14	<14	<14	<16	<12

CI = confidence interval; DRE = digital rectal examination; PSA = prostate-specific antigen; PV = prostate volume.



**Fig. 3 – The bars show the cross-validated mean percentages of cancer detected according to the number of cores at initial biopsy (8 cores: 78.3%; 10 cores: 83.4%; 12 cores: 87.5%; 14 cores: 90.9%; 16 cores: 93.8%; 18 cores: 96.2%; 20 cores: 98.2%). Box and whisker report the range and median values. Error bars report the 95% confidence intervals. The 8-, 10-, 12-, 14-, 16-, 18-, and 20-core schemes detected the following percentages of all cancer detected: 8 cores, 76.2–80.6%; 10 cores, 82.3–84.6%; 12 cores, 86.7–88.3%; 14 cores, 90.3–91.5%; 16 cores, 93.2–94.4%; 18 cores, 95.6–96.9%; and 20 cores, 97.2–99.3%.**



**Fig. 4 – The graph shows the variability of the cancer detected (expressed as standard deviations of the mean percentage of cancer detected) of all the possible combinations of sampling sites at a fixed number of cores according to different clinical characteristics and for the whole population.**

DRE = digital rectal examination; PSA = prostate-specific antigen; PV = prostate volume.

Three patients had significant rectal bleeding, which was treated by placing a tampon intrarectally. Acute prostatitis with a temperature >39 °C, requiring hospitalization, and acute urinary retention occurred in 0.4% and in 2.1% of patients, respectively.

#### 4. Discussion

Over the last few years, interest has increased in defining more efficient biopsy schemes for PCa detection [11–16]. Intuitively, adding more biopsies to prostatic areas not sampled by standard sextant schemes should increase the detection rate. The current trend is to use extended

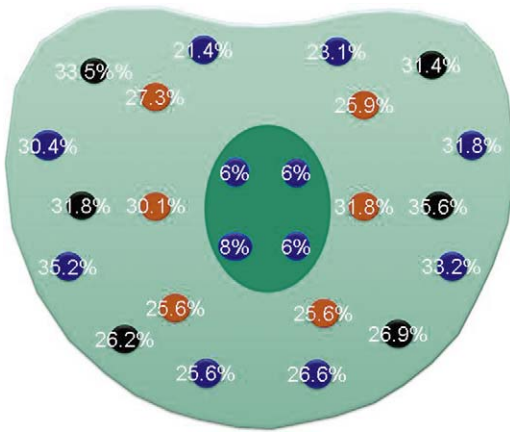


Fig. 5 – Percentage of positivity on an individual-core basis of a 24-core biopsy.

prostatic schemes (10–12-core biopsy without the transition zone) as the initial biopsy strategy. Nevertheless, the role of a saturation biopsy ( $\geq 20$  cores) as initial strategy is controversial. Eichler et al. [11] showed that no significant benefit accrues by taking  $>12$  cores, and Jones et al. [12] suggested that further efforts at extended biopsy strategies beyond 10–12 cores are not appropriate in the initial setting. More recently, Pepe and Aragona reported in a retrospective study that saturation biopsy (range: 24–37 cores) does not increase the PCa detection rate compared with an 18-core scheme in the initial setting [13]. Although saturation biopsy seems to be unnecessary as a primary approach, it is likely that the most advantageous number of biopsies is a number that ranges between 12 and 20 cores.

In the current paper, we confirmed that the larger the number of cores taken, the higher the cancer detection rate found. Guichard et al performed a saturation biopsy (21 cores) as their initial biopsy in 1000 patients including sextant biopsies, three additional posterolateral biopsies in each peripheral zone, three biopsies in each transition zone, and three biopsies in the midline peripheral zone [17]. They found an improvement, although not statistically signifi-

cant, in the detection rate when increasing from 12 to 18 or 21 cores (improvement of cancer detected of about 7% with an increase of cancer detection rate of 2.8%) [17]. We report similar findings with a continuum of improvement of the cancer detection rate when increasing the number of cores even if the cancer detection rate of the 24 cores was significantly higher only than the mean cancer detection rates of 12-core schemes. Nevertheless, it is important to notice that the French scheme [17] is different from ours because we sampled the peripheral zone more widely. We took a total of 20 cores from the peripheral gland, whereas the French group obtained only 12 cores from the peripheral gland plus 3 cores from the midline, which added little to the cancer detection rate. As a result, they reported an overall cancer detection rate of 42.5%, which is less than our overall cancer detection rate of 46.8%. In another study, Descazeaud et al reported that the detection rate of their 21-core biopsy protocol was similar to their 10- to 12-core biopsy scheme as an initial biopsy strategy [18]. Recently, Delongchamps et al evaluated saturation biopsies (36 cores) on autopsied prostates for detecting prostate cancers [19]. They concluded that the detection rate of the saturation biopsy protocol was not increased over an 18-core regimen [19]. In a large retrospective study, we previously showed that an initial 18-core prostatic biopsy did not improve the overall prostate cancer detection rate compared with a 12-core prostatic biopsy (39.9% vs 38.4%;  $p = 0.37$ ) [20]. Our data and the recently published series support the hypothesis that the saturation biopsy is unnecessary in the initial setting even if there is a continuum of improvement of cancer detection with an increasing number of cores.

We reported a difference of about 10% between the cancers detected with 24- and 14-core schemes. Even if this difference is statistically not significant, we believe that it is clinically relevant. Thus we decided to define the most advantageous number and sites of cores to reduce morbidity and costs. Interestingly, Neill et al recently reported that a protocol of medial sextant and targeted biopsy revealed about 95% of PCa that would be detected with a 10-core biopsy protocol [21]. The routine inclusion of four additional lateral prostate biopsies detected an extra

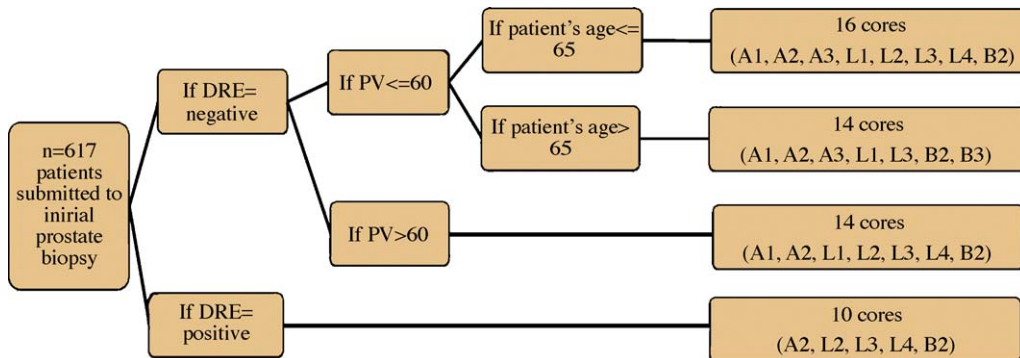
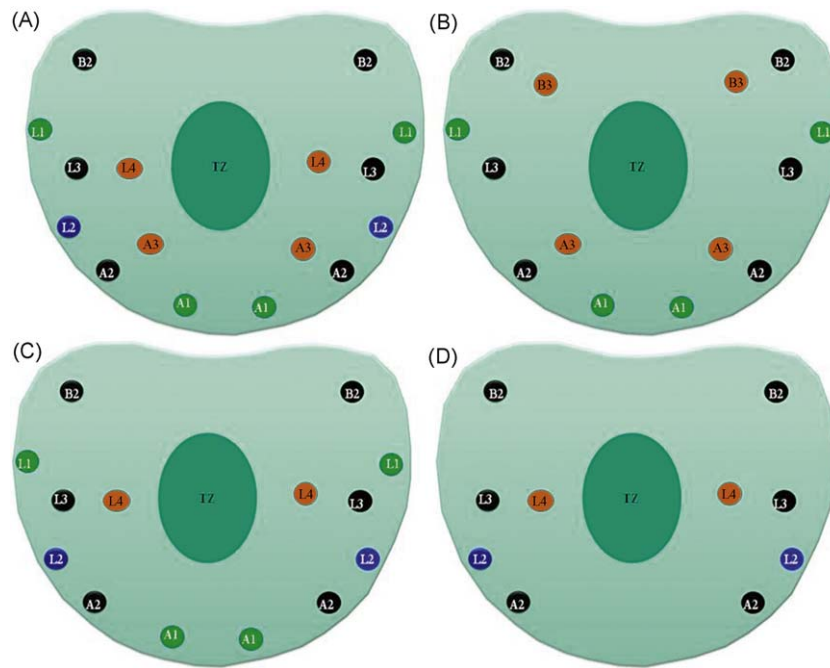


Fig. 6 – Flowchart showing location and number of cores of the scheme that detects  $>95\%$  of the cancers with the minimum number of cores, in four different risk groups (see Fig. 2 and 7 for the position of the cores). The risk groups were identified by using a classification and regression tree analysis depicting the risk to detect prostate cancer at initial biopsy. DRE = digital rectal examination; PV = prostate volume.



**Fig. 7 – The most advantageous set of the biopsy core that maximizes the cancer-detection rate with the minimum number of cores in patients with (A) a negative digital rectal examination (DRE), prostate volume (PV)  $\leq 60$  cm<sup>3</sup>, and age  $\leq 65$  yr; (B) a negative DRE, PV  $\leq 60$  cm<sup>3</sup>, and age  $>65$  yr; (C) a negative DRE and PV  $>60$  cm<sup>3</sup>; and (D) a positive DRE.**

3% clinically significant PCa while increasing staff costs by 30%. Haas et al recently performed 18-core needle biopsies on autopsy prostates from 164 men who had no history of PCa [22]. They found that 12-core biopsies were most likely to detect most of the clinically significant cancers. Even if we agree with the conclusions of Haas et al, it is necessary to consider that the two studies are different because we have taken 24 cores in referral patients with a suspicion of PCa and not in deceased men with an unknown PSA value. In contrast, Ravery et al reported that the 20-core biopsy protocol was more efficient than the 10-core biopsy protocol, especially in patients with PSA values between 3 and 6 ng/ml [23]. Nevertheless, due to the retrospective aspect of the study, the authors were unable to define the most advantageous number of cores.

In our study we have shown that the scheme that performed the best is a specific combination with 10 to 16 cores according to the clinical characteristics of the patients (Fig. 6). Moreover, we provide a user-friendly flowchart to choose the most advantageous sampling according to the risk to detect PCa at initial biopsy. For example, patients with a positive DRE may require a specific combination of only 10 cores (A2, L2, L3, L4, B2) to detect  $>95\%$  of all cancer detected. Luciani et al previously showed that in patients presenting with PSA levels  $>10$  ng/ml and abnormal DRE findings, a transperineal 6-core biopsy yielded a detection rate similar to that of a 12-core biopsy [24]. We believe that patients with a high suspicion of cancer do not systematically require extensive sampling, whereas other patients need  $>12$  cores. In a previous large retrospective study, we demonstrated that patients with a PV  $<55$  cm<sup>3</sup> or a transitional volume  $<30$  cm<sup>3</sup> do not need

an 18-core prostatic biopsy, and a 12-core prostatic biopsy may be adequate [20]. In the current population we have now demonstrated that patients with a negative DRE, PV  $\leq 60$  cm<sup>3</sup>, and age  $\leq 65$  yr require a specific 16-core scheme to maximize the detection rate (A1, A2, A3, L1, L2, L3, L4, B2) (Fig. 7D). In contrast, in patients with a negative DRE and PV  $>60$  cm<sup>3</sup> a specific combination of a 14-core biopsy (A1, A2, L1, L2, L3, L4, B2) is adequate to detect 95% of the cancer detected. Based on our results, we strongly recommend that in the future, clinical practice prostatic schemes should be individualized for each patient, as we showed in Fig. 6.

The sites that must be sampled to maximize the detection rate remain controversial. It is already known that the laterally and apically based cores improve the cancer detection rate. Haas et al demonstrated that the ability to detect prostate cancer was more related to the biopsy site than to the number of biopsy cores taken [22]. They showed that the 12-core biopsy taken from the mid and lateral peripheral zones were most likely to detect the majority of clinically significant cancers. We agree with this conclusion, but we believe that both the number and site of cores have a great impact on PCa detection. As shown in Figs. 3 and 4, we demonstrated that the variability of the detection rates according to all the possible combinations at a given number of cores depends on the clinical characteristics of the patient. In our series, the variability was higher in the group of patients with a lower suspicion of having cancer (negative DRE or PSA  $<10$  ng/ml or PV  $\leq 60$  cm<sup>3</sup>), suggesting that it is more important in these cases to choose the exact combination of sites to detect more cancers. In patients with positive DRE findings, the variability was

lower, suggesting the location is not so important at a given number of cores. Nevertheless, given the density of the cancer detection for each single core [25] and according to our results, it is better to spread the biopsies cores homogeneously in the very lateral peripheral gland and more to the apex than to the base. We believe that this study is an important addition to the accumulating evidence that it is not only increasing the number of biopsy cores taken but also targeting the appropriate locations in the prostate that will lead to the optimal detection of PCa.

Besides its strengths, the present study presents some limitations, the most obvious that we unfortunately do not know how many cancers were missed by our 24PBx scheme. Thus our study is influenced by verification bias because we cannot define the real diagnostic accuracy of our combinations of schemes. Because it is not possible to perform radical prostatectomy in all these patients and it is unjustified to perform >24 cores as an initial strategy to detect all possible cancers on the basis of the results of the literature [23], we believe it is not possible to overcome this limitation, which is common in all studies similar to ours. Moreover, we have not stratified the cancers detected into clinically significant and insignificant cancers. Because only <50% of the patients had undergone radical surgery at the study presentation, we are unable to verify how many cancers were really insignificant. Moreover, the question of the clinical significance of any diagnosed PCa is beyond the scope of the current study.

## 5. Conclusions

The mean cancer detection rates significantly increase with an increasing number of cores. At a given number of cores, the cancer detection rates vary significantly according to the different combination of sites considered. The most advantageous scheme varies according to the clinical characteristics of the patients. We propose a user-friendly flowchart to identify the most advantageous set of sampling sites according to patients' characteristics.

**Author contributions:** Vincenzo Scattoni had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Scattoni, Raber, Montorsi.

**Acquisition of data:** Scattoni, Raber, Dehò, Roscigno, Angiolilli, Maccagnano, Freschi, Doglioni.

**Analysis and interpretation of data:** Scattoni, Raber, Gallina, Montorsi.

**Drafting of the manuscript:** Scattoni, Raber, Gallina, Abdollah, Rigatti, Montorsi.

**Critical revision of the manuscript for important intellectual content:** Scattoni, Raber, Abdollah, Gallina.

**Statistical analysis:** Scattoni, Abdollah, Gallina.

**Obtaining funding:** None.

**Administrative, technical, or material support:** Doglioni, Rigatti, Montorsi.

**Supervision:** Doglioni, Rigatti, Montorsi.

**Other (specify):** None.

**Financial disclosures:** I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript

(eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

**Funding/Support and role of the sponsor:** None.

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