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Journal of the Chinese Medical Association 81 (2018) 1044−1051

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Original Article

Comparison of cancer detection between 18- and 12-core prostate biopsy in Asian patients with prostate-specific antigen levels of 4−20 ng/mL

Bo-Ren Wang [a,b,c], Cheng Che Chen [b], Ren-Hao Zheng [b], Ju-Chuan Hu [b], Yen-Chuan Ou [d,*]

[a] *Division of Urology, Department of Surgery, Taichung Arm Force General Hospital, Taichung, Taiwan, ROC*
[b] *Division of Urology, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*
[c] *National Defense Medical Center, Taipei, Taiwan, ROC*
[d] *Division of Urology, Department of Surgery, Tung's Taichung MetroHarbor Hospital, Taichung, Taiwan, ROC*

Received January 5, 2018; accepted June 1, 2018

Abstract

Background: Although prostate biopsy is an accepted option for cancer detection, there is little data regarding the clinical outcome of 18-core transrectal ultrasound (TRUS)-guided biopsy. This retrospective study compared cancer detection rates and biopsy complications between 12- and 18-core TRUS biopsy in Asian patients with prostate-specific antigen (PSA) levels between 4.0 and 20.0 ng/mL.
Methods: In total, 1120 consecutive patients with PSA levels between 4.0 and 20.0 ng/mL were divided into the 12-core (552 patients) and 18-core TRUS biopsy (568 patients) groups. The clinical outcomes of the 12- and 18-core TRUS-biopsy groups were compared. Clinical outcomes were evaluated by comparing the prostate cancer detection rates and post-biopsy complication rates.
Results: There were no significant group differences in the PSA levels, but the mean age was significantly older in the 12-core biopsy group than in the 18-core biopsy group (mean age, 67.0 vs. 64.0 years, respectively; $p = 0.001$). The abnormal digital rectal examination rate was higher in the 12-core biopsy group than in the 18-core biopsy group (39.9% vs. 24.5%, respectively; $p < 0.001$). The prostate cancer detection rate was significantly higher in the 18-core group than in the 12-core group [adjusted odds ratio: 2.75, 95% confidence interval = 2.04−3.01; $p < 0.001$], especially in patients with age $\geq$ 50 years, PSA < 10 and cancer clinical stage cT1. ($p < 0.001$). Moreover, in patients with prostate volumes >30 mL or PSA densities <0.2, the prostate cancer detection rate was significantly higher in the 18-core group than in the 12-core group. There were no differences in the complication rates (e.g., urinary retention, hematuria, urinary tract infection, and urosepsis).
Conclusion: In Asian patients with serum PSA levels between 4.0 and 20.0 ng/mL, 18-core biopsy was associated with superior clinical outcomes to those of 12-core biopsy for detecting prostate cancer.

Keywords: Asian patients; Prostate cancer; Prostate-specific antigen

1. Introduction

In 1989, Hodge et al. first proposed the ultrasound-guided sextant method for prostate biopsy, with a true-positive rate of 20%−30% and a false-negative rate of 15%−35%.[1] This six-core biopsy method has long been recognized as inadequate for cancer detection because it overlooks 15%−30% of underlying cancer.[2−4] In 1995, Stamey et al., after analyzing the histological cuts of radical prostatectomies, observed that the higher tumor volume was in the peripheral zone more lateral to the sextant plane and recommended shifting biopsies more laterally to better sample the anterior horn of the peripheral zone.[5] Ploussard et al. compared cancer detection rates (CDRs) and found that the 12-core procedure improved the CDR by 19.4% ($p = 0.004$) relative to that of the sextant approach.[6,7]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Yen-Chuan Ou, Division of Urology, Department of Surgery, Tung's Taichung MetroHarbor Hospital, 699, Section 8, Taiwan Blvd., Taichung 435, Taiwan, ROC.
E-mail address: ycou228@gmail.com (Y.-C. Ou).

https://doi.org/10.1016/j.jcma.2018.06.003

Currently, the extended 12-core systemic biopsy that incorporates apical and far-lateral cores in the template distribution is recommended by the American Urological Association (AUA).[8] Initially, we followed the 12-core biopsy method suggested by the AUA, but only an approximately 17.6% CDR was found in our clinical practice. The benefits of increasing the number of cores from 12 to 18 have not been consistently demonstrated across studies.[9,10] Although the benefit of 18-core biopsy was more evident in a randomized controlled trial study by Francisco et al., the trial was limited by the small study sample, which prompted us to investigate the problem further by incorporating more study groups and to modify the 18-core biopsy method to use a more lateral site sampling than that used in the 12-core biopsy method.[9,10]

The most widely accepted indication for prostate biopsy is a prostate-specific antigen (PSA) value of >4.0 ng/mL.[11–16] For PSA levels from 4.0 to 10.0 ng/mL, the positive predictive value has been found to be approximately 25%[17]; this increases from 42% to 64% for PSA levels >10 ng/mL.[17] Based on the preceding cited study,[17] the inclusion criteria in the present study were patients with PSA levels from 4 to 20 ng/mL to exclude mostly normal or abnormal population groups.

This retrospective study aimed to investigate the differences in clinical outcomes between 12- and 18-core biopsy. An increased number of biopsy cores may improve CDRs, but the risk of detection of insignificant prostate cancer (PCa) may also be elevated. Additionally, because of the concerns about the safety of the 18-core procedure, we also compared the complication rates between the two groups. This is the first study to specifically investigate the use of 18-core biopsy in Asian patients with serum PSA levels from 4.0 to 20.0 ng/mL.

2. Methods

From our institutional review board-approved prostate biopsy database, we reviewed 1120 patients with serum PSA concentrations from 4.0 to 20.0 ng/mL who underwent initial transrectal ultrasound (TRUS)-guided needle biopsies at our hospital during an approximately 5-year study period (January 2009–December 2014). From 2009 to 2012, most patients underwent a 12-core biopsy (six cores from the peripheral zone (PZ) and six cores from the parasagittal zone), and from 2012 to 2014, most patients underwent 18-core TRUS biopsy (eight cores from the PZ and 10 cores from the parasagittal zone). The study design designated the major core group in each period and excluded patients with PSA values <4 and >20 ng/mL. For example, from 2009 to 2011, a total of 1433 patients underwent TRUS-biopsy; of these, 720 patients underwent the 12-core method, which accounts for the most part (50.2%). We excluded patients without PSA within 4–20 ng/mL; a total of 552 patients represented this cohort. Fig. 1 illustrates a diagram summarizing our study protocol.

One day before the procedure, the patients were given a cleansing enema and prophylactic parenteral fluoroquinolone antibiotic. The antibiotic was administered for 1 day pre-procedure. The biopsy protocol included an ultrasound-guided prostate examination to detect hypoechoic areas. We used a multifrequency (5–10 MHz) biplanar side-fire probe on a BK Medical instrument (Flex Focus 1202; BK Medical, Germany) to obtain axial and sagittal images. Prostate and transition zone (TZ) volumes were calculated by using the formula for a prostate ellipsoid, (transverse width × transverse length × longitudinal height × 0.52). PSA density was calculated by dividing PSA by prostate volume. All patients were placed in the left lateral decubitus position with knee and hips flexed 90° and were administered general intravenous anesthesia. In all patients, biopsy sites were identified by using a biplane probe; samples were obtained by using an 18-gauge needle with a spring-loaded biopsy gun. As an example, the right parasagittal sample distribution in a patient from the 18-core group is shown in Fig. 2.

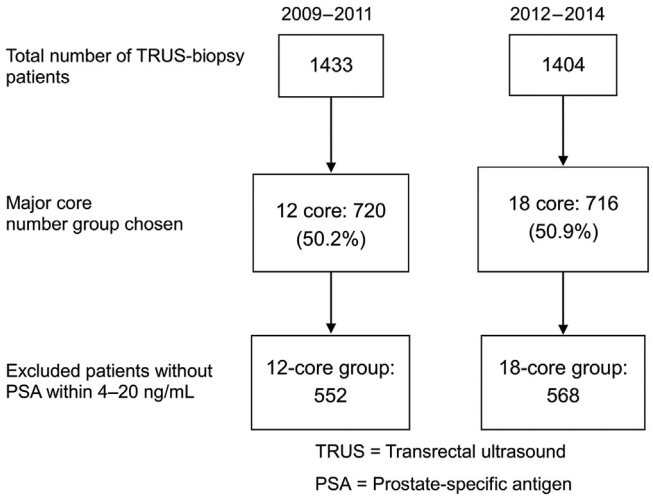


Fig. 1. Flowchart of patients at different time periods enrolled for analysis. PSA = prostate-specific antigen. TRUS = transrectal ultrasound.

The Gleason grading system is used to help evaluate the prognosis of men with prostate cancer by using samples from a prostate biopsy. The total score was calculated on the basis of how the cells looked under a microscope, with half of the score based on the appearance of the most common cell morphology (scored 1–5) and the other half based on the appearance of the highest-grade cell morphology (scored 1–5). These two numbers were then combined to produce a total score for the cancer.[18]

Insignificant PCa was defined according to the Epstein criteria[14]: PSA density (PSAD) ≤0.15 ng/mL/g, Gleason score ≤6, fewer than three positive cores, and <50% cancer involvement in any core; significant PCa was defined as that with a Gleason score of ≥8.[19]

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 4.0. Hematuria Grade III was defined as gross hematuria requiring transfusion, medication, or hospitalization and for which elective endoscopic, radiologic, or operative intervention was indicated and/or when it limited the patient's self-care activities of daily living. Grade II urinary retention was defined as urinary retention for which the placement of a urinary, suprapubic, or intermittent catheter was indicated or for which

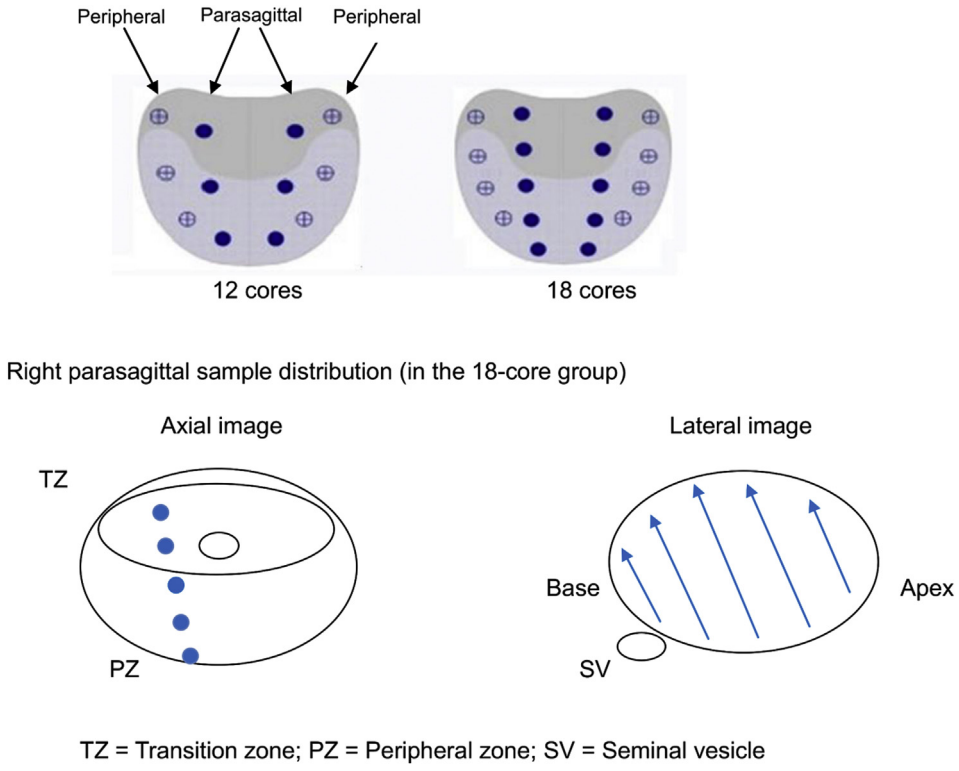


Fig. 2. Sampling sites in 12- and 18-core prostate biopsy.

the administration of medication was indicated. Urinary tract infection complication is defined as a disease characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra.

2.1. Statistical analysis

The differences in distributions between the 12-core group and 18-core group were examined by using an independent *t*-test for continuous variables and the chi-square test for categorical variables. The associations between the PCa detection rates and the 12-core and 18-core groups were assessed by using an adjusted odds ratio (aOR) and 95% confidence interval (CI) with logistic regression. Analyses were performed by using the Statistical Package for the Social Sciences (IBM SPSS version 22.0; International Business Machines Corp, New York, USA) for data management and statistical analyses. A p value of ≤ 0.05 was considered as indicating statistical significance. Statistical bias was corrected, and Software G power 3.1.3. (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was used to compute effect sizes and to graphically display the results of power analyses.

3. Results

The patient characteristics of the two core biopsy groups are listed in Table 1. Compared with the patients in the 18-core biopsy group, those in the 12-core biopsy group had (a) a higher mean age (67.0 vs. 64.0 years, $p = 0.001$), (b) a higher PSAD (0.17 vs. 0.16 ng/mL/cc, $p = 0.006$), (c) a lower prostate volume (45.6 vs. 48.8 mL, $p = 0.011$), and (d) a higher abnormal digital rectal examination (DRE) rate (39.9% vs. 24.5%, $p < 0.001$) (Table 1). No 5α-reductase inhibitor or androgen deprivation therapies were used in any of the patients.

Overall, 552 and 568 patients were divided into the 12- and 18-core biopsy groups, respectively, and cancer was detected in 97 and 188 patients in the 12-core and 18-core biopsy groups, respectively. The PCa detection rate was significantly higher in the 18-core biopsy group than in the 12-core biopsy group (33.1% vs. 17.6%; aOR: 2.75; 95% CI = 2.04–3.01; $p < 0.001$). The power was calculated as 1.00 according to the core number data by using software G power 3.1.3. For the

Table 1
Characteristics of patients in the 12- and 18-core biopsy groups.

	12 core (n = 552)		18 core (n = 568)		p
	Median	IQR	Median	IQR	
Age	67.00	(60.00–74.00)	64.00	(59.00–71.00)	0.001**
PSA (ng/ml)	7.72	(5.97–11.00)	7.46	(5.82–10.83)	0.239
PSA density (ng/ml/cc)	0.17	(0.12–0.26)	0.16	(0.11–0.23)	0.006**
F-PSA	1.16	(0.81–1.63)	1.15	(0.83–1.65)	0.963
Prostate volume (ml)	45.65	(33.75–61.22)	48.80	(35.20–66.00)	0.011*
TZ	30.80	(20.80–41.30)	45.00	(35.15–89.85)	0.021*
Abnormal DRE (n, %)[a]	220	(39.9%)	139	(24.5%)	<0.001**
F-PSA, %	0.20	(0.16–0.31)	0.19	(0.16–0.27)	0.576

F = free; PSA = prostate specific antigen; TZ = transition zone; DRE = digital rectal examination.
*$p < 0.05$, **$p < 0.01$.
[a] Chi-square test.

patients who were positively diagnosed as having PCa, the prostate volume was significantly smaller (<30 vs. ≥30 mL; aOR: 0.59; 95% CI = 0.39−0.89; $p < 0.012$). In the patients who were positively identified as having PCa, the PSAD was significantly higher (≥0.2 vs. <0.2; aOR: 1.41; 95% CI = 1.02−1.95; $p = 0.039$). Fig. 3 shows the positive core sites in the 12- and 18-core biopsy groups; there was no significant difference in the positive core sites between the groups.

Comparison of age, PSA, PSA density, prostate volume, and clinical stage in 12- and 18-core biopsy-positive patients revealed that the cancer detection rate was significantly higher with 18-core biopsy than with 12-core biopsy, especially in patients with age ≥50 years, PSA <10 and cancer clinical stage cT1. ($p < 0.001$) (Table 2). Among patients with prostate volumes >30 mL, cancer was detected in 65 (29.8%) and 153 (70.2%) patients from the 12-core and 18-core biopsy groups, respectively ($p < 0.001$, chi-square test) (Table 2). We also found that for the patients with PSADs <0.2, cancer was detected in 37 (24.2%) and 112 (75.8%) patients from the 12-core and 18-core biopsy groups, respectively ($p = 0.001$, chi-square test) (Table 2).

The percentages of patients with different PCa grades are shown in Table 3. These data show that there were no higher rates of insignificant cancer according to the Epstein criteria, atypical small acinar proliferation, or high-grade prostatic intraepithelial neoplasia. The 18-core biopsy increased the detection of both higher-grade PCa (Gleason score 7, Gleason score 8, and Gleason score 9−10) and significant PCa (Gleason score ≥8) (9.9% vs. 2.4%; $p < 0.001$)

Regarding adverse events, no significant difference in complication rates (such as urinary retention or urosepsis) was found between the two groups. Only one patient who underwent 18-core biopsy developed severe urosepsis and died because of multiple organ failure. This 51-year-old patient had a history of hypertension and gout and presented with high fever and irritable consciousness 1 day after the biopsy procedure. Dyspnea and desaturation developed, and the patient received intubation with ventilator support. The disease progressed due to sepsis, and acute renal failure occurred following which hemodialysis was performed. He died 10 days after the biopsy procedure due to multiple organ failure, including adult respiratory distress syndrome (ARDS), renal failure, and heart failure. Final blood and urine culture yielded bacteria with extended-spectrum β-lactamases (Table 4).

4. Discussion

Patients in the 12-core group were older, had a larger PSAD, a lower prostate volume, and a higher abnormal DRE rate than those in the patients in the 18-core biopsy group. Because of the differences in the basic patient data, we consulted with a statistical specialist to correct for bias in interpreting the results. In the adjusted data, the 18-core biopsy still demonstrated a better cancer detection rate than that of the 12-core biopsy. Other demographic features, such as PSA, F-PSA, and the cancer detection rate in TZ biopsy, were not significantly different between the groups. Detection of PCa was significantly better in the 18-core group, specifically in patients with prostate volume >30 mL or PSAD <0.2[20,21] than in the 12-core group.

According to the National Comprehensive Cancer Network guideline, insignificant PCa mostly can be treated with active surveillance or observation; however, high-grade PCa or

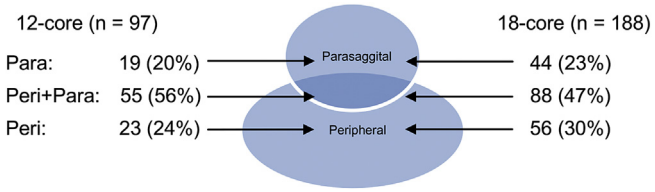


Fig. 3. The positive core sites in 12- and 18-core biopsies.

Table 2
Comparison of age, PSA, PSA density, prostate volume, and clinical stage in 12- and 18-core biopsy-positive patients.

Variables	12 core (n = 97)		18 core (n = 188)		p
	n	%	n	%	
Age (years)					
<50	0	0%	10	100.0%	–
≥50	97	35.3%	178	64.73%	<0.001**
PSA (ng/ml)					
4−9.9	56	30.11%	130	69.89%	<0.001**
10−20	41	42.71%	55	57.29%	0.153
PSA density (ng/ml/cc)					
<0.2	37	24.20%	116	75.80%	<0.001**
≥0.2	60	45.50%	72	54.50%	0.296
Prostate volume (ml)					
≤30	32	47.80%	35	52.20%	0.714
>30	65	29.80%	153	70.20%	<0.001**
Clinical state					
T1	41	23.03%	137	76.97%	<0.001**
T2	53	53.00%	47	47.00%	0.549
T3-4	3	42.86%	4	57.14%	0.705

PSA = prostate-specific antigen.
Chi-square test. *$p < 0.05$, **$p < 0.01$.

Table 3
Comparison of the percentages of different prostate cancer grades between patients who underwent 12-core and 18-core biopsy.

	12 core (n = 552)		18 core (n = 568)		p
	n	%	n	%	
Gleason score					
≤6	58	10.51%	73	12.85%	0.190
7	26	4.71%	59	10.39%	<0.001**
8	7	1.27%	21	3.70%	0.008
9-10	6	1.09%	35	6.16%	<0.001**
Group					
ASAP	13	2.40%	10	1.80%	0.532
HGPIN	11	2.00%	7	1.20%	0.346
Group					
Insignificant PCa	16	2.90%	30	5.30%	0.039*
Significant PCa (GS ≥ 8)	13	2.40%	56	9.90%	<0.001**

Chi-square test. *$p < 0.05$, **$p < 0.01$.
ASAP = atypical small acinar proliferation; GS = Gleason score; HGPIN = High-Grade Prostatic Intraepithelial Neoplasia; PCa = prostate cancer.
Insignificant prostate cancer: Prostate-specific density (PSAD) ≤ 0.15 ng/mL per gram, Gleason score (GS) ≤ 6, fewer than three positive cores and <50% cancer involvement in any core.

Table 4
Comparison of complication grades between 12-core and 18-core biopsy.

Variables	12 core (n = 552)	18 core (n = 568)	p
	n (%)	n (%)	
Urinary retention (Grade II)	4 (0.7%)	7 (1.2%)	0.389
Hematuria (Grade III)	8 (1.4%)	10 (1.8%)	0.679
UTI	3 (0.5%)	5 (0.9%)	0.503
Urosepsis	0 (0.0%)	1 (0.2%)	0.324
Mortality	0 (0.0%)	1 (0.2%)	0.324

UTI = urinary tract infection.
Chi-square test.

significant PCa mostly needs to be treated with radical prostatectomy, radiotherapy, or hormone therapy. Consequently, higher CDR in high-grade PCa or significant PCa may prompt early interventional therapy.

We predicted the possibility of insignificant PCa in this study by using the Epstein criteria[22] and compared the insignificant CDRs between the 12-core and 18-core biopsy groups. Our data showed that the insignificant cancer detection rate was not higher in the 18-core biopsy group than in the 12-core biopsy group. There was no evidence that 18-core biopsy clinically elevated insignificant cancer detection. Yasuhide et al.[23] and Li et al.[24] also reported that the insignificant cancer detection rate was not higher in the extended biopsy group. However, Francisco et al.[10] reported that although there was no statistically significant difference in detection rates, clinically insignificant PCa was diagnosed more often in their extended biopsy group (5.9% vs 14.3%, p = 0.38); therefore, the risk of detecting clinically insignificant PCa should not be neglected when using extended biopsy.

Our study also found a higher detection rate for higher-grade PCa (Gleason score 7, 8, and 9–10) and significant PCa (9.9% vs 2.4%, $p < 0.001$) in the 18-core group than in the 12-core group. Li et al.[24,25] reported that an increase to ≥20 prostate biopsy samples to achieve saturation increased the detection rate of clinically significant PCa, but there was no statistically significant difference in the detection of higher-grade cancer. All of these studies have concluded that increasing the number of biopsy cores significantly increased PCa detection rates. Although there have been few other relevant studies to determine if an increased number of biopsy cores can improve detection rates for higher-grade PCa or significant PCa, our study provides evidence that 18-core biopsy can improve the detection rate for significant PCa without increasing that of insignificant PCa.

We also found no between-group differences in terms of complication rates (e.g., hematuria, urinary retention, or sepsis) in our study. The results were consistent with those of previous studies.[10,23] In our case, one patient experienced complications due to sepsis involving multiple organ failure, including pneumonia complicated with ARDS, renal failure, and heart failure. Therefore, further study is warranted to determine whether prostate biopsy will increase mortality rate. Gallina et al.[26] reported a large, population-based study evaluating mortality in men undergoing prostate biopsy between 1989 and 2000 in Canada. A higher, overall 120-day mortality rate was observed in 22,175 patients who underwent biopsy compared with the 1778 controls (1.3% vs. 0.3%, respectively; $p < 0.001$). Multivariable analysis revealed that increasing age and comorbidity were independent predictors of mortality. Two other reports involving large study groups from the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) screening trials reported contrasting results. The 120-day mortality rate among screen-positive patients undergoing prostate biopsy was similar to that of screen-negative patients in the ERSPC and lower than that of screen-negative patients in the PLCO study.[26]

Although the optimum number of cores for prostate biopsy remains unclear,[27,28] many studies have shown that extended prostate biopsies are superior to 12-core protocols for detecting PCa. For example, consistent with our present results, Yasuhide et al.[23] and Li et al.[24] reported that an increase in the number of prostate biopsy cores would increase PCa detection rates.[23,24,29] A randomized study reported by Francisco et al.[15] also supported that extending the sampling protocol from 12 to 18 cores at initial prostate biopsy improved the CDRs (Table 5).

On the other hand, Vincenzo et al.[9] in 2008 conducted a study similar to ours (comparing 12 and 18 prostate biopsy cores) but arrived at the opposite conclusion (Table 5).[9,30–32] This discrepancy in results could be related to sampling at the same position in other studies rather than extending the biopsy core to different sites, as we did in our study. The biopsy location, particularly including the PZ, is therefore more important than the number of biopsies taken (Fig. 4, Table 6).[9,10] In a randomized multicenter study, Irani et al.[33] reported that there was no

Table 5
Comparison of previously published evaluations of different core biopsy numbers and their associated cancer detection rates.

	Number of patients	Core numbers		Higher detection rate		Risk for prostate cancer
Abd et al.[30]	1546	12	8		No	Age, BMI
Jean et al.[31]	269	12	8		No	N/A
Rochester et al.[32]	244	15	12		No	N/A
Vincenzo et al.[9]	3460	18	12	No	Yes (V > 50 mL)	N/A
Zhang Feng-bo et al.[29]	252	24	14		Yes	N/A
Francisco et al.[10]	150	18	12		Yes	N/A
Irani et al.[33]	339	20	12		No	N/A
Li et al.[24]	3776	≥20	10–14		Yes (PSA < 10)	N/A
Yasuhide et al.[23]	332	16	12	No (slightly higher)	Yes (V > 30 mL, PSAD < 0.2)	N/A
Present study	1120	18	12	Yes	Yes (V > 30 mL, PSAD < 0.2)	PSAD, Volume, Abnormal DRE

BMI = body mass index; DRE = Digital rectal examination; PSAD = prostate-specific antigen density; V = prostate volume.

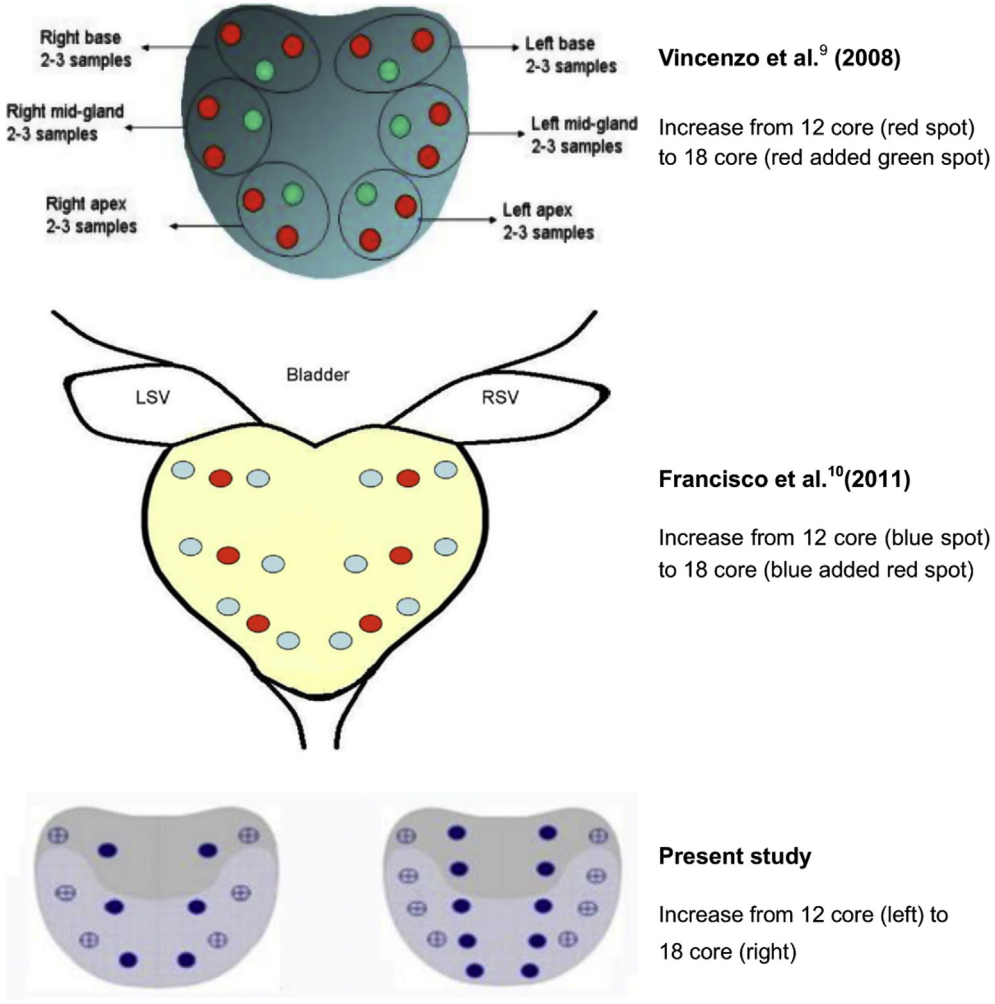
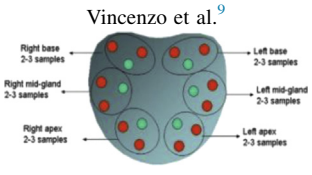
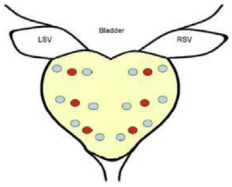


Fig. 4. Comparison of previous publication findings that evaluated increased biopsy sampling from 12 to 18 cores.

Table 6
Comparison of previous publications that evaluated increased biopsy sampling from 12 to 18 cores.

	Vincenzo et al.[9]		Francisco et al.[10]		Present study	
						
Number of patients	3460		150		1120	
Age, years	12 core	18 core	12 core	18 core	12 core	18 core
	65.9 ± 7.7	65.3 ± 7.2	64.5 ± 7.26	65.08 ± 6.82	66.72 ± 10.21	65.06 ± 9.30
PSA (ng/mL)	12 core	18 core	12 core	18 core	12 core	18 core
	7.12 ± 2.8	7.07 ± 2.7	8.89 ± 3.83	8.40 ± 3.60	8.86 ± 3.75	8.65 ± 3.75
Study design	retrospective		randomized trial		retrospective	
Cancer detection rate	12 core	18 core	12 core	18 core	12 core	18 core
	38.4%	39.9%	30.7%	48%	17.6%	33.1%
Increased detection?	No	Yes (V > 55 mL)	Yes		Yes	Yes (V > 30 mL, PSAD < 0.2)
Biopsy location	same		different		different	

PSA = prostate-specific antigen; PSAD = prostate-specific antigen density; V = prostate volume.

significant advantage in using an extended 20-core biopsy protocol instead of a 12-core protocol during an initial prostate biopsy, but they also stated that no group was superior to the other and that their findings did not necessarily mean that a 12-core biopsy was inferior to the 20-core biopsy with respect to the cancer detection rate; the results could have been caused by low statistical power.

Our study had several limitations that should be addressed. In particular, this was a retrospective non-randomized study, and the choices of 12-core or 18-core biopsy were based on the investigating physicians' discretion, which led to some substantial differences (i.e., younger age and larger prostate volume in the 18-core group and higher abnormal DRE rate in the 12-core group) between the two groups. Therefore, a multicenter, large-scale, prospective, randomized trial of 18-core biopsy will be of higher scientific value. Nonetheless, to the best of our knowledge, this was the first reported study to focus specifically on 18-core biopsy in Asian population. Our study demonstrated a better cancer detection rate than that of 12-core biopsy. Despite the study limitations, the study provides evidence that an 18-core biopsy is as safe as a 12-core biopsy.

In conclusion, the clinical outcomes of 18-core biopsy for detecting PCa in Asian patients with serum PSA levels from 4.0 to 20.0 ng/mL were found to be superior to those of 12-core biopsy. However, larger scale, randomized controlled trials are warranted to confirm the efficacy and safety of 18-core PCa biopsy.

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