Anterior Apical Cores in the Initial Prostate Biopsy do not Increase Detection Rate of Significant Prostate Cancer

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Purpose: To examine the effect of routine sampling anterior apical cores in the initial prostate biopsy among patients that 14-cores of prostate biopsy (PB) planned.

Materials and Methods: Five-hundred twenty-eight patients with increased prostate-specific antigen (PSA) levels and/or abnormal digital rectal examination underwent transrectal ultrasound and initial PB between November 2012 and October 2013. We performed routine 12-cores extended PB, plus 2 anterior apex samples that were taken from the junction of urethra and apex of the prostate. Site-specific and unique cancer detection rate, tumor characteristics, the presence of clinically insignificant prostate cancer (PCa) (clinical stage ≤ T1, serum PSA level of < 10 ng/mL, biopsy Gleason score ≤ 6, number of positive biopsy cores ≤ 3 and no core with > 50% involvement) and biopsy-related pain were evaluated.

Results: PCa was detected in 147 of 451 patients (32.6%). The lateral base of the prostate was the most affected area with 128 of 451 patients (28.3%), followed by unique cancer detection, with 17 of 40 patients (43.5%). Anterior apex (n = 6) was in third place after the lateral apex (n = 8). The patients diagnosed by anterior apex cores were all clinically insignificant PCa. The cancer diagnosis rate would be 31% if 12-cores biopsy was used, but the rate was found to be 32.6% in 14-cores biopsy (P = .016). Average biopsy pain, right anterior apex biopsy pain, and left anterior apex biopsy pain were found to register at 0.61, 1.06 and 1.08 points in the visual analog scale pain score, respectively. When right and left anterior apex biopsy pain is compared to average biopsy pain, the pain level was found to be statistically significantly higher in the biopsies of right and left anterior apex (P = .040 and P = .042, respectively).

Conclusion: The gold standard for the diagnosis of PCa is at least 8 cores PB. According to our results, although most PCa diagnosis is carried out with 14-cores PB, it should not be forgotten that these patients might have clinically insignificant PCa.

Keywords: prostatic neoplasms; diagnosis; biopsy; needle; methods; prostate; pathology.

INTRODUCTION

There were 679,000 new cases of prostate cancer (PCa) worldwide in 2002.[1] Estimated age-standardized incidence rates were 119.9 and 61.6 per 100,000 male population in the United States and Europe, respectively.[1] Transrectal ultrasound guided (TRUS) prostate biopsy (PB) is suggested as the gold standard for the diagnosis of PCa.[2,3] At least 8 cores PB is recommended by European Association of Urology (EAU) guidelines, and there is no consensus about the number of optimal cores.[2] Performing PB with a greater number of cores is considered to increase the cancer detection rate, despite increasing the rate of adverse effects. However, this hypothesis is controversial, as it is the first PB, and has not yet been verified.[1,4-8] The examination of radical prostatectomy and cystoprostatectomy specimens has proved that the detection of PCa is more related to the location of the cores than the number of the cores conducted in PB.[9,10] For this reason, many authors recommend that the peripheral zone, in which most cases of PCa develop, be sampled appropriately.[9,11,12] It was advocated that the traditional sextant PB yields poor sampling for anterior of prostate.[13] Several studies have recommended anterior apex sampling to increase PCa detection rate.[14] During a digital rectal examination (DRE), there may be difficulties in palpating the apical anterior cancers that extend and develop at the apex of the peripheral prostate zone from anteriorly to the distal prostatic urethra.[14,15] Instead of passing through the rectum, the apical core biopsies may transverse the anus, which is sensitive to pain because of the sensorial pain fibers, therefore these biopsies are considered as more painful, and as a result, some urologists might avoid this procedure to minimize pain.[16]

In this study, the primary aim was to examine the effect of taking cores of anterior apical on the initial diagnosis of PCa among patients waiting to undergo 14-cores of TRUS PB. The secondary aim was to determine the pain levels that related to additional anterior apical biopsies.

MATERIALS AND METHODS

Study Participants

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Table 1. Demographic and clinical characteristics of study subjects.

Variables	Total	Benign	Cancer	*P* Value
Number of patients (%)	451	304 (67.4)	147 (32.6)	____
Patients' age (year), mean ± SD (range)	63.33 ± 6.27	62.13 ± 6.11	65.81 ± 5.88	< .05
	(40-75)	(40-75)	(49-75)	
IPSS, mean ± SD (range)	10.30 ± 6.88	10.09 ± 6.65	10.71 ± 7.32	.377
	(0-33)	(0-27)	(0-33)	
Serum PSA (ng/mL), mean ± SD (range)	9.84 ± 7.74	8.41 ± 5.60	12.80 ± 10.32	< .05
	(1.16-47.5)	(1.16-37.3)	(2.66-47.5)	
PSA Subgroups				
< 10 ng/mL, n (%)	308 (68.3)	232 (51.4)	76 (16.9)	
10-20 ng/mL, n (%)	88 (19.5)	47 (10.4)	41 (9.1)	< .05
21-50 ng/mL, n (%)	55 (12.2)	25 (5.5)	30 (6.7)	
Prostate volume (cm^3), mean ± SD (range)	45.20 ± 25.16	49.35 ± 26.49	36.60 ± 19.62	< .05
	(10.39-216.25)	(12.57-216.25)	(10.39-129.44)	
DRE Abnormality, n (%)				
Yes	69 (15.3)	25 (5.5)	44 (9.8)	< .05
No	382 (84.7)	279 (61.9)	103 (22.8)	
Total cores length (mm), mean ± SD (range)	18.30 ± 3.24	18.03 ± 3.26	18.84 ± 3.12	.012
	(6.60-29.10)	(6.60-29.10)	(9.90-26.10)	

Abbreviations: PSA, prostate-specific antigen; DRE, digital rectal examination; IPSS, International Prostate Symptom Score; SD, standard deviation.

All 4052 patients, who underwent TRUS PB between September 2007 and June 2014, were included in a prospectively collected database. The study, conducted between November 2012 and October 2013, included 528 patients with the serum prostate specific antigen (PSA) level over 2.5 ng/mL, or with an abnormality in DRE, and who were waiting to undergo TRUS PB for the first time. Thirteen patients aged over 70 years and with serum PSA level under 10 ng/mL, 8 patients with the life expectancy of less than 10 years and 56 patients with the serum PSA level over 50 ng/mL were excluded from the study (**Figure**). The life expectancy was determined by the nomogram for PCa.[17] The demographic and tumor-related data of the patients were assessed. PB was conducted with an 18-gauge core biopsy needle in an appropriate outpatient operation room and under appropriate antibiotic prophylaxis, by using the end fire ultrasound probe and after performing periprostatic nerve block with 10 mL 1% of lidocaine. All TRUS PB was performed by the same experienced urologist. Each core was put into tubes containing 10% of formaldehyde, and labeled with locations from which they were taken. Each core was evaluated by the same experienced pathologist (UB), according to the Gleason grading system. Clinically insignificant PCa was defined as clinical stage ≤ T1, PSA < 10 ng/mL, biopsy Gleason score ≤ 6, number of positive biopsy cores ≤ 3, and no core with > 50% involvement. The study protocol was approved by the local ethics committee, and informed consents were provided by all patients.

Table 2. Comparison of VAS scores between prostate cancer and benign groups.

Variables	Total	Benign	Cancer	*P* Value*
DRE	1.15 ± 1.83	1.15 ± 1.74	1.14 ± 2.00	.920
Probe insertion	3.03 ± 2.63	3.04 ± 2.46	3.00 ± 2.95	.872
Periprostatic nerve block	0.47 ± 1.11	0.48 ± 1.11	0.46 ± 1.11	.875
12-core biopsy	0.61 ± 1.23	0.59 ± 1.19	0.65 ± 1.30	.604
Right anterior apex biopsy	1.06 ± 1.49	1.12 ± 1.49	0.93 ± 1.49	.215
Left anterior apex biopsy	1.08 ± 1.55	1.16 ± 1.58	0.90 ± 1.48	.100

Abbreviations: VAS, Visual Analog Scale; DRE, digital rectal examination.
* *P* values between prostate cancer and benign groups.

Prostate Biopsy Procedure

Three cores from lateral apex, mid-gland, and base of the prostate in the lateral plane and 3 cores from lateral apex, mid-gland, and base of the prostate in the parasagittal plane were taken from the right side of all patients. Then the same procedure was performed on the left side. Following this, the anterior apex samples were taken from the junction of urethra and apex. Firstly, right anterior apical core was taken and the same procedure was performed on the left side. In order to evaluate the biopsy-related pain, 10 points of linear visual analog scale (VAS) were used by the physician during the

Table 3. Comparison of tumors between located unique anterior apex and other tumors.

Variables	Total	Unique Anterior Apex	Other Tumors	*P* Value
Number of patients with adenocarcinoma (%)	147	6 (4.1)	141 (95.9)	____
Serum PSA (ng/mL), mean ± SD (range)	12.80 ± 10.32	4.92 ± 1.37	13.13 ± 10.4	< .05
	(2.66-47.5)	(3.06-6.67)	(2.66-47.50)	
Prostate volume (cm^3), mean ± SD (range)	36.60 ± 19.62	41.81 ± 4.51	36.38 ± 19.98	.045
	(10.39-129.44)	(34.56-47.98)	(10.39-129.44)	
Number of positive cores, mean ± SD	4.97 ± 4.32	1 ± 0.0	5.13 ± 4.34	< .05
Total cores length (mm), mean ± SD (range)	18.84 ± 3.12	19.26 ± 2.06	18.83 ± 3.16	
	(9.90-26.10)	(17.60-22.90)	(9.90-26.10)	.740
Tumor length (mm), mean ± SD (range)	2.82 ± 4.03 (1.00)	0.15 ± 0.17	2.94 ± 4.08	< .05
		(0.07)	(1.08)	
Gleason score of patients (n)				
3+3	97	6	91	
3+4	13		13	
4+3	17		17	
4+4	10		10	
4+5	7		7	
5+4	3		3	

Abbreviations: PSA, prostate-specific antigen; SD, standard deviation.

Table 4. Frequency of prostate cancer detection among all biopsy sites.*

Variables	Number of Positive Core	Number of Unique Positive Core
14-Core Biopsy Scheme		
Right lateral apex	53 (11.8)	7
Right lateral mid	61 (13.5)	1
Right lateral base	60 (13.3)	7
Right medial apex	36 (8.0)	____
Right medial mid	50 (11.1)	2
Right medial base	46 (10.2)	____
Left lateral apex	51 (11.3)	1
Left lateral mid	57 (12.6)	2
Left lateral base	68 (15.1)	10
Left medial apex	49 (10.9)	2
Left medial mid	62 (13.7)	____
Left medial base	49 (10.9)	1
Right anterior apex	46 (10.2)	3
Left anterior apex	42 (9.3)	3
Unified Biopsy Site		
Lateral apex	104 (23.0)	8
Lateral mid	118 (26.1)	3
Lateral base	128 (28.3)	17
Medial apex	85 (18.8)	2
Medial mid	112 (24.8)	2
Medial base	95 (21.0)	1
Anterior apex	88 (19.5)	6

* Data are presented as no (%).

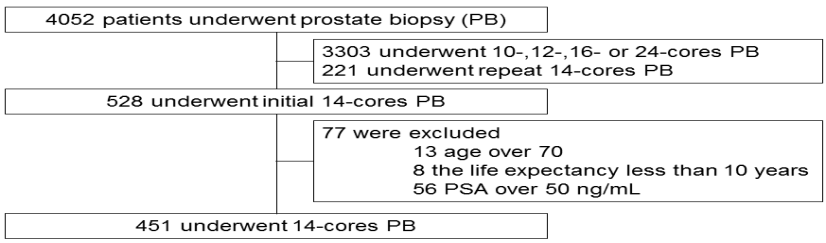

Figure. Prostate biopsy cohort flow chart.

procedure. The pain caused by the rectal probe entrance during the periprostatic block, and during the standard 12-cores biopsy conduction was evaluated. In addition, the pain levels during the right and left anterior apical cores conduction were recorded separately.

Statistical Analysis

For the parametric conditions, student's *t*-test for non-parametric conditions Mann-Whitney *U* test and for qualitative data the χ^2 test or Fisher exact test were used. The possibility of the biopsy diagrams detecting PCa was conducted with McNemar's test. *P* value < .05 was considered as statistically significant. All data were analyzed using Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 19.0.

RESULTS

Four-hundred fifty-one patients were included in the study. TRUS PB and basic data of the study group is shown in the **Table 1**. The average age of patients was 63.33 years (range, 40-75). The average International Prostate Symptom Score (IPSS) of patients were found as 10.30 (range, 0-33). Nine patients had urethral catheters, therefore their IPSS could not be evaluated. The average serum PSA value was 9.84 ng/mL (range, 1.16-47.5), and the average prostate volume was determined as 45.20 cm^3 (range, 10.39-216.25).

The average probe pain was determined as 3.03, the average biopsy pain following periprostatic nerve block was determined as 0.61, and there was statistically significant difference between the conditions (*P* < .05). The average anterior apex biopsy pain was 1.06 on the right side and 1.08 on the left. When both were compared separately to average biopsy pain, pain levels were found to be higher and statistically significant (*P* = .040 and *P* = .042). There was no statistically significant difference in VAS scores between detected PCa and benign groups (**Table 2**).

The total core of TRUS PB length was identified as 18.30 mm (range, 6.60-29.10). Of the total number of patients undergoing biopsy, 147 (32.6%) were diagnosed with PCa (**Table 3**). PCa was detected in an average of 4.97 (range, 1-14) cores. Serum PSA values of 147 (32.6%) patients were examined in PCa detected group, and it was seen that 76 (51.8%) were under 10 ng/mL, and 41 (27.8%) were between 10-20 ng/mL and 30 (20.4%) were between 20-50 ng/mL. When a subgroup of the patients diagnosed with PCa was examined, it was found that the Gleason score of 64 patients (43.5%) was 6 and the serum PSA level was under 10 ng/mL.

According to the 14 cores PB diagram, cancer was detected in the left lateral base core in 69 of the 451 patients, and this area has the highest PCa detection rate, with 15.1% (**Table 4**). The cancer detection rate was to be found 10.2% for the right anterior apex, and 8.3% for the left. When biopsy sites were assessed in combination, the contribution of the lateral cores to PCa diagnosis found that the highest and most important was the lateral base core, with 28.3%. The contribution of anterior apex to diagnosis was found to be 19.5%. In 88 of 450 patients diagnosed PCa in the anterior apex cores, the Gleason score of anterior apex cores were correlated with other detected cancer cores. There was no upgraded the Gleason score due to the anterior apex biopsy. Thirty-nine patients (8.6%) were detected with unique PCa involvement when one core was examined, and among these, the left lateral base yields the highest rate of detecting PCa, with a total of ten patients. When the results are examined according to the unified biopsy site, while the lateral base (n = 17) was found the highest in diagnosing, anterior apex (n = 6) remained in third place after the lateral apex. In addition, in one patient, PCa was detected in both left and right anterior apex. Thirty-seven patients (94.8%) were diagnosed with unique PCa, and Gleason score was 3+3 PCa. For the other two patients, Gleason score was found as 4+3 PCa. Lateral base core had the highest rate of detecting unique PCa (n = 17). If a 12-cores PB was conducted, PCa diagnosis rate would be 31%, and by adding the anterior apex PB, this rate increased to 32.6%, which was found to be statistically significant (*P* = .016). For all 6 patients diagnosed by anterior apex cores, Gleason score was found 6, and average serum PSA value was 7.53 ± 7.01 ng/mL (range, 3.06-21.18). For the patient diagnosed with PCa by both anterior apex, serum PSA value was found to be 21.18 ng/mL, the maximum percentage of PCa in the core was 70%, and the Gleason score was 3+3. This patient underwent radical retropubic prostatectomy, and Gleason score was raised to 4+3. When the seven patients diagnosed with PCa by only anterior apex were compared with another 140 patients diagnosed with PCa, there were no statistically significant differences in age (*P* = .154), serum PSA level (*P* = .167), DRE findings (*P* = .675), prostate volume (*P* = .730), VAS score, total average of core length (*P* = .976) and Gleason score (*P* = .096), the only significant difference was in the IPSS (3.71 vs. 11.07, *P* < .05). When comparing the patients diagnosed with PCa in anterior apex with other patients diagnosed with PCa in standard 12-core, there were no statistically significant differences in variables.

DISCUSSION

The diagnosis of PCa depends on adequately sampling the zones in which cancer is mostly located. Early and decisive diagnosis rate has considerably risen in the last 20 years due to sextant biopsy protocol. Two basic modalities, i.e. the change of biopsy location and increase of total biopsy cores, have been applied in order to prevent high false-negative.[1,8] Nowadays, even if there is no consensus about the ideal schema for the initial PB, most authors recommend minimum 8-cores PB.[1,2,8,12]

It is considered that core location is more important for detection of PCa. According to our knowledge, apical anterior gland was not sampled in past biopsy regimens. Anterior compartment of prostate includes anterior horns of the peripheral, anterior transitional and fibromuscular zones. Chen and colleagues tested biopsy strategies with a computer simulation model using 180 radical prostatectomy specimens. According to this, the highest PCa detection rate was found in the anterior horn.[18] The study of Bott and colleagues investigated over 547 radical prostatectomy specimens, and indicated that 21% of PCa was found to have mainly anterior distribution.[19]. Many other studies also have confirmed that clinically significant PCa exists in the anterior of the prostate. Takashima and colleagues examined tumor maps of 62 Japanese patients, whose clinical stage was T1c using a computer-assisted imaging technique.[13] Even though an equal distribution of PCa between anterior and posterior was found, the authors indicated that nonpalpable lesions are denser on the apex, and the primary extent of these tumors was in the anterior half of the prostate. They found that the efficiency of traditional sextant PB is low for determination of PCa settling as anterior. Eskicorapci and colleagues presented PCa detection rates in different zones of prostate, and 42.6% involvement in the prostate apex was detected.[20]

Wright and Ellis proposed anterior apical biopsy because it increases total cancer detection, and they found that unique cancer detection rate of anterior apical biopsy was 17%.[21] This was a retrospective study with 12-cores PB, and also included first or repeating biopsy. However, apical biopsies have been conducted from under 3-5 mm of the prostatic apex. In contrast to our study, clinically significant PCa was detected by unique anterior apical biopsy, and no differences could be found in terms of serum PSA level, Gleason score, prostate volume and clinical stage.[21] Although apical anterior sampling results in a slight increase in total PCa diagnosis, which has no statistical significance, Meng and colleagues stated that it was possible to diagnose 2% of patients with only apical anterior biopsy.[22] This contribution has become prominent in men whose prostate volume was under 50 cc, serum PSA value was low and had a normal DRE. Orikasa and colleagues examined the first or repeating PB data of 931 Japanese patients retrospectively, and in 252 patients who had undergone their first PBs, PCa detection rate was 51% on the apical anterior peripheral zone. Despite only a slight increase in total PCa diagnosis detected with apical anterior biopsy, this increase was approximately 5.2% in first biopsy patients.[23] This effect has been found statistically significant in patients with a prior negative and normal DRE. Patient groups of these studies must be examined carefully, because the significance of the anterior apex might be different in the first and repeating biopsy. Supporting this view, Presti states that even in the case that apex and lateral apex are sampled using extended PB, these additional cores are important, especially in repeating biopsies.[24]

Moussa and colleagues have prospectively evaluated 181 patients whose initial PB was performed. They indicated that 14-cores PB determined significantly greater levels of PCa than 12-cores PB (47.5% vs. 44.2%). They found that the tumor features of PCa, which were detected to a limited extent on anterior apex, were similar to other PCa.[14] In another study, Sazuka and colleagues evaluated factors that predict preoperative tumor on prostate apex via radical prostatectomy specimen in 158 Japanese patients. PSA value, Gleason score, tumor stage and total tumor volume were not found to be preoperative factors that predict positive PB on the apex.[25] In another recently published retrospective study, Gleason score ≥ 7 was found to be more likely to be detected with 14-cores PB.[26] We showed increased cancer detection rate with 14-cores PB, and unlike other studies, we detected clinically insignificant PCa with additional anterior apical cores. On the other hand, 37 of the 39 patients (94.8%) with unique PCa were clinically insignificant PCa. In patients with a unique PCa, PCa is often in small volume (< 0.5 mL), therefore these cases tend to be insignificant.

Most urologists believe that apical PB is more painful, due to the pain fibers of the inferior rectal nerve below the dentate line. In a study involving 60 patients, Jones and Zippe have indicated that avoiding this nerve with rectal sensation test significantly decreases VAS score (1.25 vs. 2.28) of apical PB.[16] Meng and colleagues stated that anterior apical biopsy is tolerated well, and anterior apical sampling causes no increase in pain levels.[22] However, in this study, no method for evaluating pain, such as VAS, was used. In contrast, in our study, it was found that anterior apical biopsy VAS score was almost 55% greater than normal biopsy VAS ($P < .05$).

Limitations of our study include its retrospective nature, the use of a single tertiary institution and a single racial group. In this study, the complication rate has not been examined. Pain assessment was performed during procedure. The duration of the pain was not taken into consideration. For Patients on whom PCa was detected, it is not clear whether or not these cancers are clinically significant, as radical prostatectomy was not performed on all. However, in the literature, study population in this area focuses on Japanese and American populations, therefore, this study presents different patients from a different racial background. Although the addition of anterior apex to initial PB increases the diagnosis of PCa, patients who were diagnosed with PCa with anterior apical cores in the first PB were clinically insignificant PCa.

CONCLUSION

According to our results, although greater levels of more detailed/accurate PCa diagnosis can be achieved with 14-cores PB, it should not be forgotten that patients who were diagnosed PCa with anterior apical cores in the first PB, potentially may have clinically insignificant PCa. It should also be kept in mind that the addition of anterior apex cores to routine 12-cores PB increases the pain of the PB procedure.

CONFLICT OF INTEREST

None declared.

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