an automatic biopsy gun with an 18 gauge needle. Additional biopsies were added if suspicious areas were noted on transrectal ultrasound or digital rectal examination. The prostate was imaged in the transverse and sagittal planes with the patient in the lithotomy position. Prostate and TZ volumes were determined using the formula for a prolate ellipsoid, (width × length × height × $\pi/6$).[3] PSAD and PSATZD were calculated by dividing the PSA value by prostate volume and by the TZ, respectively. Repeat biopsies included systemic sextant biopsies with an additional 6 cores from the TZ.

Tissue component of prostate transition volume. We selected 2 biopsy cores from the TZ for this study. The cores were stained with hematoxylin and eosin, and were subjected to morphometry processed in uniform fashion using computer assisted image analysis. Under 100× magnification using a BH-2 light microscope (Olympus Optical Co., Tokyo, Japan) with a PXC-S500 charge coupled device digital camera (Sony, Tokyo, Japan) 4 areas of each core were saved in a hard disk as a JPEG image. If cancer was located in the TZ, the area of cancer was excluded from the image. A single urologist blinded to any information about clinical data performed the morphometric measurement. The percent areas of gland component and lumen were measured using National Institutes of Health Image 1.61 image analysis software (URL: http://rsb.info.nih.gov/nih-image/) (fig. 1). The percent area of epithelium was determined by subtracting the percent of lumen from that of the glandular component. TZ epithelial volume was calculated by multiplying TZ volume by the percent of epithelium. PSATZepiD was calculated as serum PSA divided by TZ epithelial volume. Seven whole mount specimens obtained from patients who underwent retropubic radical prostatectomy were also subjected to this morphometric measurement. The percent areas of each component on the largest TZ area plane were measured.

Statistical analysis. Results are presented as the mean ± SD. Variables in the different groups were compared using the Mann-Whitney U test with $p < 0.05$ considered statistically significant. The relationships between serum PSA, and total prostate volume, TZ volume and TZ epithelial volume were determined using simple regression analysis. The significance of PSA based parameters for predicting prostate cancer was assessed based on ROC curves, which are plots of the positive rate (sensitivity) vs the false-positive rates (1 − specificity) using all possible different cutoff values. The AUC was calculated and compared as described by Hanley and McNeil.[4] Independent factors for detecting prostate cancer were identified by multivariate logistic regression analysis. The predicted probability of prostate cancer (P) was estimated using the formula, $p = 1/(1 + exp[-k])$. Logistic regression produces a score of k, where $k = a + b1X1 + b2X2 + \ldots + bnXn$, which is a linear combination of the predictors (X1, X2, . . . Xn) in the model. The model coefficients (a, b1, b2, . . . , bn) are chosen to optimize the ability of the model to predict the probability of prostate cancer.[5] Multivariate logistic regression used backyard stepwise selection of variables for inclusion or exclusion at the Pz ≤0.05 cutoff.

RESULTS

Table 1 shows the results of subset analysis in 75 patients with serum PSA between 4.0 and 10.0 ng /ml at repeat biopsy. Cancer was detected on repeat biopsy in 19 of 75 patients (25%). Of these 19 men with prostate cancer, 13 had cancer in the PZ only, 5 had cancer in the PZ and TZ, and 1 had cancer in the TZ only.

The free-to-total ratio was significantly lower in patients with vs without prostate cancer. PSA-ACT was significantly higher in patients with vs without prostate cancer. Prostate volume in the 2 groups did not differ significantly, while TZ volume was significantly smaller in patients with vs without prostate cancer. There were no significant differences in total PSA in men with and without cancer.

Of the tissue components patients with prostate cancer had a significantly larger percent of fibromuscular stroma and a smaller percent of epithelium or glandular lumen than those without cancer. PSATZD and PSATZepiD were significantly higher in patients with prostate cancer. However, PSAD was not significantly different between the 2 groups.

Figure 2 shows the correlation between serum PSA and total prostate volume, TZ volume or TZ epithelial volume in men without prostate cancer. Only TZ epithelial volume significantly correlated with total PSA. For the correlation between serum PSA and total prostate volume, TZ volume and TZ epithelial volume $r^2 = 0.048$, 0.029 and 0.122, respectively.

ROC analysis was performed in 75 patients with PSA between 4.0 and 10.0 ng/ml (table 2). PSATZepiD was found to be the best predictor of prostate cancer on ROC analysis. Area under the ROC curves for PSATZepiD was 0.879. Figure 3 shows ROC curves for total PSA, the free-to-total ratio, PSA-ACT, PSAD, PSATZD and PSATZepiD.

To determine the ability of the independent variables to eliminate patients with a benign condition from undergoing unnecessary biopsy sensitivity was set at 85%, 90% and 95%.

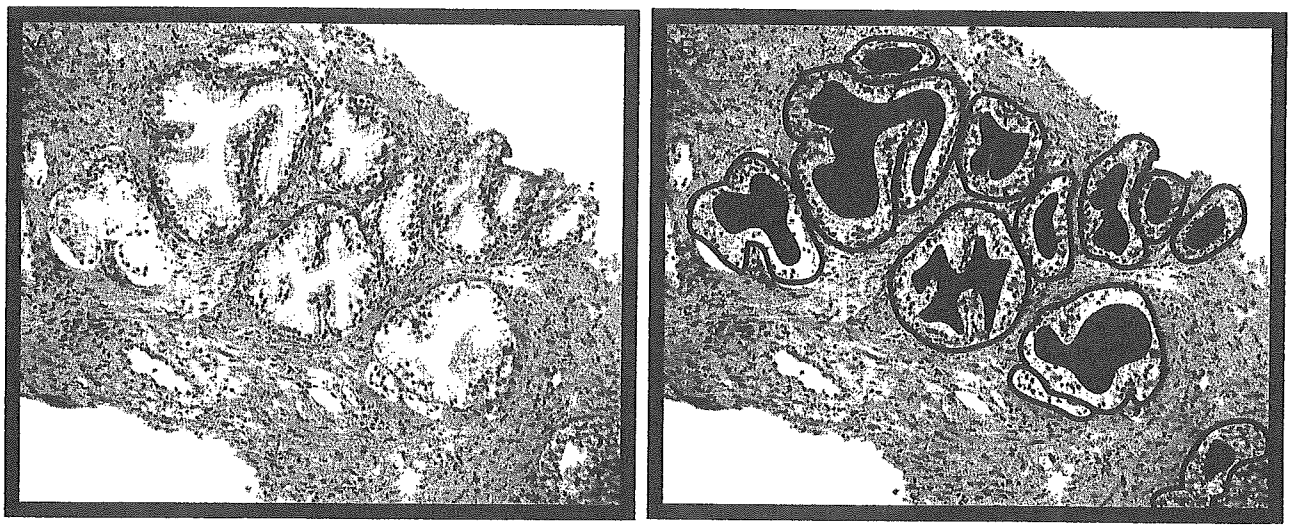

FIG. 1. Digital image analysis of prostate biopsy specimen. Percent area densities of gland component (black outlines) and glandular lumen (gray area) were measured using National Institutes of Health Image 1.61. Epithelial area was calculated by subtracting lumen area from gland area.

TABLE 1. *Patient characteristics stratified by repeat biopsy results*

	Overall	Mean Repeat Biopsy Result ± SD		
		Ca	No Malignancy	p Value
No. pts	75	19	56	
Age	67.6 ± 6.7	69.6 ± 5.7	66.9 ± 6.7	0.181
Total PSA (ng/ml)	7.58 ± 1.37	8.04 ± 1.18	7.42 ± 1.4	0.122
ACT-PSA complex (ng/ml)	6.16 ± 1.49	7.18 ± 1.87	5.81 ± 1.16	0.006
Free/total PSA	0.189 ± 0.107	0.153 ± 0.066	0.201 ± 0.116	0.033
Total prostate vol (cm^3)	40.8 ± 14.1	38 ± 10.9	41.8 ± 15	0.414
TZ vol (cm^3)	20.3 ± 9.2	16.4 ± 6.5	21.6 ± 9.7	0.030
% TZ area:				
Stroma	60.4 ± 12.6	74.2 ± 7.4	55.7 ± 10.4	<0.0001
Epithelium	26.5 ± 9.5	18.1 ± 5.6	29.3 ± 8.8	<0.0001
Lumen	13.3 ± 6.5	7.7 ± 4.9	15.2 ± 5.9	<0.0001
TZ epithelial vol (cm^3)	5.15 ± 2.47	2.94 ± 1.58	5.9 ± 2.27	<0.0001
PSAD (ng/ml/cm^3)	0.204 ± 0.076	0.226 ± 0.064	0.197 ± 0.079	0.048
PSATZD (ng/ml/cm^3)	0.46 ± 0.244	0.564 ± 0.229	0.425 ± 0.241	0.033
PSATZepiD (ng/ml/cm^3)	0.878 ± 0.506	1.408 ± 0.688	0.698 ± 0.244	<0.0001

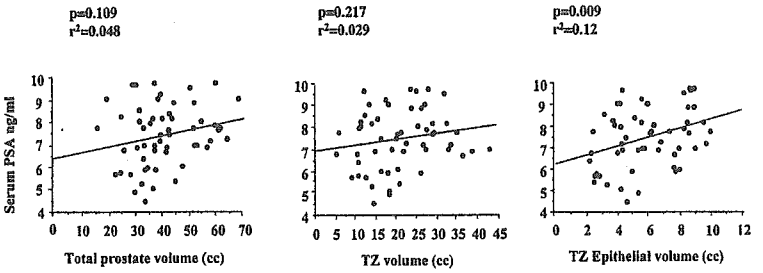

FIG. 2. Correlation between serum PSA and total prostate, TZ or TZ epithelial volume

TABLE 2. *Area under ROC curve for various parameters*

Factor	Mean AUC ± SEM
PSA	0.630 ± 0.071
Free/total PSA	0.685 ± 0.074
PSA-ACT	0.714 ± 0.077
PSAD	0.652 ± 0.073
PSATZD	0.712 ± 0.067
PSATZepiD	0.879 ± 0.051

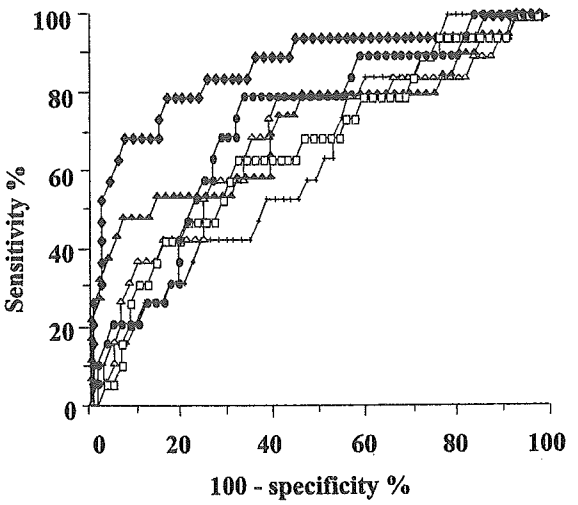

FIG. 3. ROC curves for detecting prostate cancer in 75 patients with PSA between 4.0 and 10.0 ng/ml at repeat biopsy. Plus signs indicate total PSA. Open triangles indicate free-to-total PSA ratio. Filled triangles indicate ACT-PSA complex. Squares indicate PSA density. Circles indicate PSA adjusted for TZ volume. Diamonds indicate PSA adjusted for TZ epithelial volume.

Assuming 90% sensitivity (2 cancers missed) in the analysis of 75 patients, PSATZepiD would have spared 51 of 56 unnecessary biopsies (91% specificity). On the other hand, total PSA, the free-to-total ratio, PSA-ACT, PSAD and PSATZD would have spared 14 (25%), 9 (17%), 10 (18%), 15 (27%) and 21 unnecessary biopsies (39%), respectively (table 3). Stepwise logistic regression analysis using all parameters for predicting prostate cancer confirmed that PSATZepiD was the most significant predictor of cancer detection at repeat biopsy (OR 89.8, 95% CI 9.0 to 898, p <0.0001).

To test the reproducibility and accuracy of tissue sampling we measured the histological components of prostatectomized whole mount specimen and compared them with those of biopsy. Seven of 19 patients with prostate cancer underwent prostatectomy at our institution after cancer detection at repeat biopsy. Figure 4 shows the correlation between the 2 values. They had a close correlation (r^2 = 0.846), although the comparison number was not enough.

DISCUSSION

A highly statistically significant relationship between prostate volume and serum PSA has been reported in a population based study.[6] In patients with benign prostatic hyperplasia (BPH) most PSA leakage from the prostate into serum comes from the TZ.[7] Therefore, TZ volume has a greater correlation with serum PSA than does total prostate volume. PSATZD has been suggested to improve the specificity of prostate carcinoma detection in patients with intermediate PSA levels.[8] Lepor et al reported that the highest significant correlation among PSA related values adjusted for volume was observed between serum PSA and TZ epithelial volume.[2] According to their findings epithelial volume in the PZ did not correlate well with serum PSA, although PZ has a greater epithelial area.

In the current study serum PSA in the patients without cancer only correlated significantly with TZ epithelial volume but not with total prostate volume and TZ volume.

TABLE 3. *Diagnostic validity of PSA based parameters for discriminating prostate cancer from BPH on repeat biopsy*

Parameter	85% Sensitivity		90% Sensitivity		95% Sensitivity	
	Cutoff	% Specificity	Cutoff	% Specificity	Cutoff	% Specificity
PSA (ng/ml)	7.0	39	6.4	25	6.1	23
Free/total ratio	0.21	33	0.25	17	0.27	11
PSA-ACT (ng/ml)	5.00	23	4.60	18	4.60	14
PSAD (ng/ml/cm^3)	0.157	29	0.151	27	0.139	23
PSATZD (ng/ml/cm^3)	0.323	43	0.319	39	0.252	16
PSATZepiD (ng/ml/cm^3)	2.330	93	2.281	91	2.100	79

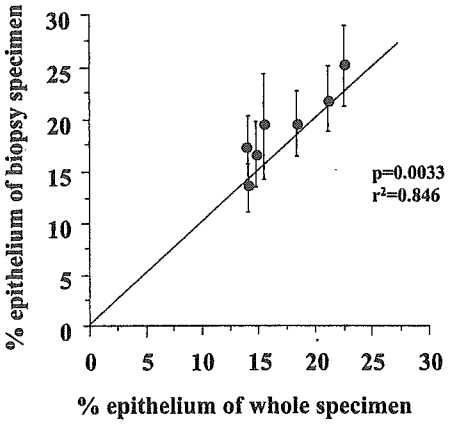

FIG. 4. Correlation between percent epithelial area of biopsy specimen and of whole mount prostatectomy specimen. Points represents mean ± SD.

Because the number used in the analysis was relatively small and the population was limited to patients with PSA between 4.0 and 10.0 ng/ml, the variation of tissue components among patients may have been the cause of these findings. It was reported that the stromal-to-epithelial ratio of the prostate varies markedly among patients.[9] Therefore, PSATZepiD could be more stable than PSAD or PSARZD in patients without cancer.

The current study shows that TZ volume, TZ epithelial volume and TZ gland volume were significantly smaller in patients with vs without prostate cancer undergoing repeat biopsy. Therefore, PSA adjusted for these volumes was considered to be more valuable for detecting prostate cancer. On ROC analysis PSATZepiD had a greater AUC than the other PSA based parameters (table 3). If the cutoff value were set at 90% sensitivity, it would eliminate more than 90% of patients with a benign condition from undergoing unnecessary biopsy (table 4). In addition, multiple logistic regression analysis using all parameters for predicting prostate cancer confirmed that PSATZepiD was the most significant independent predictor of cancer detection at repeat biopsy. The results of the current study illustrate the advantage of PSATZepiD among other PSA based parameters.

Under sampling of larger prostates may contribute to lower cancer detection in men with a larger epithelial volume. Generally the increased core biopsy regimen detected significantly more cancers than laterally sextant biopsy. Norberg et al observed that 8 core biopsies detected more cancers than standard sextant biopsy in a prospective study.[10] However, patients with a prostates of more than 40 ml had statistically the same benefit from the increased core regimen as those with a gland of less than 40 ml. Moreover, Ung et al reported that they were not able to improve the cancer detection rate in larger prostates despite increasing the number of cores from 6 to as high as 18.[11] Therefore, under sampling is not likely to be a main factor for the lower cancer detection rate in patients with a larger epithelial volume.

Because of the heterogeneity of prostatic tissue components, it is naturally questionable that the TZ core biopsy specimen should represent all TZ components. McNeal and Noldus reported that biopsy studies are not reliable for BPH tissue components.[12] However, findings in several studies suggest that biopsy specimens can be representative of the distribution of tissue components of that area.[13,14] Our results that the tissue components in the biopsy specimen correlate well with those in the whole mount seem to support their findings.

Another concern is racial differences. Since it has been reported that Asian men have a smaller prostate than white American men,[15] this volume adjusted PSA value may only be effective in Japanese or Asian men. Oesterling et al reported that age specific reference ranges for PSAD are higher in Japanese men than in white men.[16] On the other hand, Japanese men have more glandular components than American men.[17] Based on their data TZ epithelial volume is the same in Japanese and American men. Thus, PSATZepiD may be used in other races in addition to Japanese men. However, clearly these findings require larger prospective validation studies performed in men of other races.

In addition to PSA based parameters, it was reported that high grade PIN on initial biopsy and older age are also associated with cancer at repeat biopsy.[18] It has been reported that immunohistochemical staining with EPCA is highly positive in even a noncancerous core from patients with prostate cancer. Recently it became possible to measure benign PSA (BPSA) separately. Prostate cancer does not alter the relative proportions of BPSA in serum at less than 10 ng /ml.[19] In patients without prostate cancer serum BPSA has been shown to have an age independent, log linear relationship to TZ volume and it was a better predictor of prostatic enlargement than PSA or free PSA.[20] However, none of these parameters has shown higher specificity than PSATZepiD in the current study.

In this study the measurement of TZ epithelial area and cancer detection were performed simultaneously at repeat biopsy because TZ zone biopsy was not included routinely at the first sextant biopsy. If the first biopsy includes the core from the TZ, PSATZepiD can be a powerful tool for determining the indication for repeat biopsy.

CONCLUSIONS

The results of the current study indicate that PSATZepiD provides the most predictive information on prostate cancer in men who have previously undergone negative prostate biopsies and in whom PSA remains between 4.0 and 10.0 ng/ml. Although larger prospective studies are needed, patients with a low PSATZepiD value could possibly be followed less frequently and less aggressively, avoiding unnecessary repeat biopsy.

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Original Article

Efficacy and morbidity of transrectal ultrasound-guided 12-core biopsy for detection of prostate cancer in Japanese men

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Abstract

Background: The objectives of the present study were to determine whether an extensive biopsy scheme contributes to enhanced detection of prostate cancer in Japanese men and to assess the associated pain and morbidity.

Methods: A total of 147 patients were included in this analysis, with 12 biopsy cores being obtained from each patient. Standard systematic sextant biopsy at the apex, mid-prostate and base of the prostate gland was carried out under local anesthesia and this was followed by the acquisition of additional sextant cores at the same levels from the far lateral peripheral zone. Each patient answered a self-administered questionnaire on pain and morbidity during the 5 days following biopsy.

Results: Overall, 39 patients (26.5%) received a diagnosis of prostate cancer. Nine patients (23.1%) were positive only at the standard sextant sites, three patients (7.7%) were positive exclusively at the far lateral sites and the remaining 27 patients (69.2%) were positive at both sites. Cancer was found most frequently in cores obtained from the apex ($P = 0.009$), with this trend being more evident in patients with abnormal rectal findings, positive sonographic findings, gland volume < 40 cm^3 and prostate-specific antigen density > 0.15 ng/mL/cm^3 ($P < 0.03$). These findings were also true for those with a prostate-specific antigen range from 4.1 to 20.0 ng/mL. A gradual decrease in incidence and grade of pain, hematuria and rectal bleeding was observed during the first 5 days after biopsy ($P < 0.0001$).

Conclusions: Using this 12-core biopsy scheme, we found cancer most frequently in cores taken at the level of the apex. While the extensive procedure only marginally enhanced overall detection of prostate cancer, it was well tolerated with gradually decreasing pain and morbidity over a brief postbiopsy period. Further efforts to optimize biopsy schemes are warranted.

Key words early detection, morbidity, prostate cancer, prostate specific antigen, sextant biopsy.

Introduction

Transrectal ultrasound-guided systematic sextant biopsy is considered the standard procedure for detecting prostate cancer.[1] Although sextant biopsy provides safe and easy access to the prostate gland, this strategy may miss clinically significant cancer in 17% to 30% of patients.[2–5]

Attempts to avoid these false-negative findings have led to numerous studies of alternative site sampling or extensive biopsy strategies that have demonstrated prostate cancer detection rates higher than that of standard sextant biopsy.[6–11] Terris *et al.* showed that adding lateral sextant biopsy detected cancer in an additional 15% of their total patient population.[7] Levine *et al.* reported a 30% improvement in cancer detection through the use of two sets of sextant biopsies.[8] Gore *et al.* likewise observed that 12-core biopsy had a better

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detection rate than traditional sextant biopsy.[11] On the other hand, Naughton *et al.* suggested that 12-core biopsy and sextant biopsy have almost equivalent cancer detection rates.[9] Whether results from Western countries are directly applicable to the Japanese male population is not known, owing to the differences between countries in practice patterns and tumor characteristics at diagnosis.[12]

Previously study has shown that transrectal sextant biopsy plus two additional cores from the lateral peripheral zone (PZ) does not substantially enhance cancer detection in Japanese men.[13] Moreover, the 8-core biopsy scheme was accompanied by an increased incidence of bacteremia and resultant high fever. Thus, the optimal biopsy strategy, including number of cores and appropriate sites in the Japanese male population, remains to be established.

The objectives of the present study are to determine whether additional far-lateral biopsy in the PZ contributes to enhanced detection of prostate cancer and to assess morbidity during the first 5 days following biopsy.

Patients and methods

Patients and biopsy technique

We prospectively studied 160 consecutive patients who underwent transrectal 12-core extensive biopsies at Kitasato University Hospital, Kanagawa, Japan, between June 2000 and March 2001. Thirteen patients had previously been diagnosed and treated for prostate cancer and were therefore excluded from the study. Of the remaining patients, 134 (83.8%) had not previously undergone biopsy and 13 (8.1%) had previously undergone at least one biopsy with negative findings.

All patients whose digital rectal examination results appeared questionable and/or who had serum prostate-specific antigen (PSA) levels greater than 2.0 ng/mL by Dainapack AxSYM PSA assay (Dinabot, Tokyo, Japan) underwent biopsy. For some patients, the indication for biopsy arose in part from pretreatment evaluation for benign prostatic hypertrophy, rather than findings specifically related to possible cancer.

The Bruel & Kjaer 1846 console (Gentofte, Denmark) equipped with a 7 MHz multiplanar transducer was used for all ultrasound examinations and biopsies. All patients received transrectal ultrasound-guided biopsies under local anesthesia.[14] Five minutes prior to biopsy, a 21-guage needle was used to infiltrate approximately 5 mL of 1% lidocaine around each periprostatic neurovascular bundle at the base, mid-prostate and apex levels. Prostatic cores were obtained using an 18-gauge needle driven by a spring-loaded Bard Biopty-gun (Covington, GA). Needles were fired at the prostatic margin at an angle of approximately 30 degrees to the rectal wall. Standard transrectal systematic sextant biopsy was followed by acquisition of additional biopsy cores from sites in the far lateral PZ chosen to maximize its sampling (Fig. 1). One patient required an additional core from a hypoechoic lesion that appeared suspicious on ultrasound, while all other hypoechoic lesions were sampled by the 12 standard cores. Patients received standard antibiotic prophylaxis consisting of 100 mg ciprofloxacin on the morning of biopsy and three times a day for the next 2 days.

Assessment of patients with prostate cancer

Clinical stage was assigned in accordance with the unified tumor node metastasis (TNM) system.[15] All histology slides were examined and reviewed by a single pathologist (SK) and tumor grade was assigned based on the Gleason grading system. Prostate-specific antigen density (PSAD) was derived by dividing serum PSA by prostate volume, as determined by transrectal ultrasonography (prostate length × width × height × $\pi/6$).

Biopsy findings were correlated with the clinical findings at each biopsy site. Subgroup analysis was conducted to identify the most frequent site of cancer detection using the 12-core biopsy scheme.

Questionnaire on pain and adverse events

Patients subsequently completed a self-administered questionnaire on pain and adverse events, including

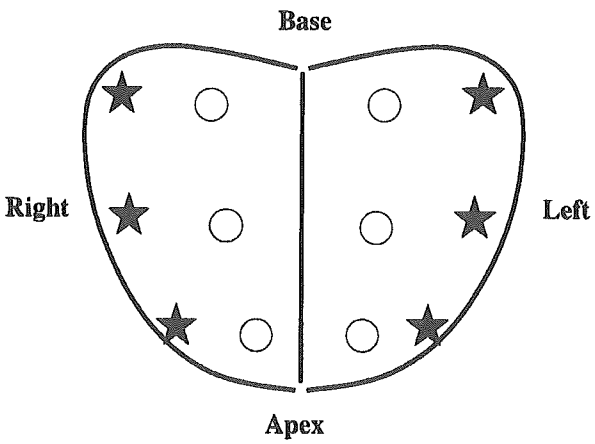

Fig. 1 Sites of standard sextant (○) and lateral sextant (★) prostatic biopsy.

hematuria, rectal bleeding, hematospermia and fever, during the 5-day period following biopsy (See Appendix). Pain was graded on a scale of 0 (no pain) to 10 (most severe). For presentation purposes, pain intensity was further stratified arbitrarily into mild (less than 4), moderate (4 through 6) and severe (greater than 6). Patients were also asked to rate the grade of each adverse event.

Statistical analysis

Differences between clinical characteristics and among biopsy outcomes were assessed using the Mann–Whitney *U*-test, Fisher's exact test or χ^2 test, with $P < 0.05$ as significant. Changes in pain scale and adverse events with time and differences in the number of positive cores at each biopsy site were assessed using the Friedman test or χ^2 test. All analyses were performed using the StatView statistical package (StatView version 5.0 for Windows. SAS Institute Inc., Cary, NC).

Results

Patient characteristics

The median age of the 147 eligible patients was 67 years (range, 39–90 years; Table 1). Men with prostate cancer were significantly older than those with benign histology ($P = 0.0002$). The median PSA and PSAD values were 5.8 ng/mL (range, 0.9–676) and 0.16 ng/mL/cm^3 (range, 0.034–7.69), respectively. Patients with prostate cancer had significantly higher PSA (14.7 versus 4.8 ng/mL, $P < 0.0001$) and greater PSAD (0.71 versus 0.13 ng/mL/cm^3, $P < 0.0001$) than those with benign histology. Patients with benign histology had significantly larger prostate glands (36.4 versus 27.3 cm^3, $P = 0.004$) and transition zones (15.6 versus 11.2 cm^3, $P = 0.017$) than those with prostate cancer.

Cancer detection and characteristics according to clinical findings

Overall, 39 of the 147 patients (26.5%) had prostate cancer (Table 2). Prostate cancer was detected in 38 of 134 (28.4%) patients with no previous history of biopsy and in 1 of 13 (7.7%) with at least one previous negative biopsy. Patients with abnormal rectal findings, positive sonographic findings (hypoechoic lesion), smaller gland volume and higher PSAD were significantly more likely to have prostate cancer ($P < 0.05$). Positive biopsy rates in patients with PSA 2.1–4.0 ng/mL, 4.1–10.0 ng/mL, 10.1–20.0 ng/mL and ≥20.1 ng/mL were 5.1%, 19.7%, 30.0% and 79.2%, respectively ($P < 0.0001$). No cancer was diagnosed in patients with PSA ≤ 2.0 ng/mL.

The incidence of extraprostatic disease (>T3) and poorly differentiated lesions (Gleason score >7) in these PSA ranges were 0%, 0%, 8.3%, 0% and 26.3%, and 0%, 0%, 8.3%, 16.7% and 68.4%, respectively (Table 2). Distant metastases were found in 15.4% of patients in the current series.

Cancer location in 12-core biopsy

Nine cancers (23.1%) were identified only in cores from the standard sextant sites, three (7.7%) were positive exclusively in cores from the far lateral PZ sites and the remaining 27 (69.2%) were positive in cores from both sites (Table 3). Table 4 stratifies the details of cancer location according to clinical findings. Cancer was found more frequently at the apex in both standard sextant and far lateral PZ cores ($P = 0.009$). This finding is stronger in patients with abnormal rectal findings, positive sonographic findings, gland volume <40 cm^3 and PSAD >0.15 ng/mL/cm^3 ($P < 0.03$). Statistical significance was not achieved in the subgroup with PSA > 10 ng/mL. The findings were the same for those without previous biopsy as for the overall group.

Table 1 Clinical characteristics of patients

	Number of patients	Median (range)				
		Age (years)	PSA (ng/mL)	PSAD (ng/mL/cm^3)	TZ volume (cm^3)	Prostate volume (cm^3)
Overall	147	67 (39–90)	5.8 (0.9–676)	0.16 (0.034–7.69)	13.2 (1.5–105.3)	33.6 (9.8–128.5)
Cancer	39	70 (51–90)	14.7 (2.8–676)	0.71 (0.068–7.69)	11.2 (3.9–49)	27.3 (16.6–90)
No cancer	108	65 (39–85)	4.8 (0.9–62.5)	0.13 (0.034–4.66)	15.6 (1.5–105.3)	36.4 (9.8–128.5)
P-value	–	0.0002	<0.0001	<0.0001	0.017	0.004

PSA, prostate specific antigen; PSAD, prostate specific antigen density; TZ, transition zone.

Table 2 Clinicopathological findings of prostate cancer detected by transrectal ultrasound-guided 12-core biopsy

	Number of patients (%) PSA (ng/mL)					
	<2.0	2.1–4.0	4.1–10.0	10.1–20.1	>20.1	Total
Biopsy results						
Positive	0 (0.0)	2 (5.1)	12 (19.7)	6 (30.0)	19 (79.2)	39 (26.5)
Negative	3 (100)	37 (94.9)	49 (80.3)	14 (70.0)	5 (20.8)	108 (73.5)
T-stage						
T1c	–	2 (100)	8 (66.7)	3 (50.0)	3 (15.8)	16 (41.0)
T2a	–	–	1 (8.3)	3 (50.0)	5 (26.3)	9 (23.1)
T2b	–	–	2 (16.7)	–	6 (31.6)	8 (20.5)
T2c	–	–	–	–	–	–
T3a	–	–	1 (8.3)	–	1 (5.3)	2 (5.1)
T3b	–	–	–	–	2 (10.5)	2 (5.1)
T4	–	–	–	–	2 (10.5)	2 (5.1)
M-stage						
M0	–	2 (100)	10 (83.3)	6 (100.0)	12 (63.2)	30 (76.9)
M1	–	–	–	–	6 (31.6)	6 (15.4)
Mx	–	–	2 (16.7)	–	1 (5.3)	3 (7.7)
Gleason score						
2–4	–	1 (50.0)	5 (41.7)	–	1 (5.3)	7 (17.9)
5–6	–	1 (50.0)	6 (50.0)	5 (83.3)	5 (26.3)	17 (43.6)
7	–	–	–	–	11 (57.9)	11 (28.2)
8–10	–	–	1 (8.3)	1 (16.7)	2 (10.5)	4 (10.3)

PSA, prostate specific antigen.

Table 3 Cancer detection stratified by PSA range and biopsy sites

Biopsy site	Number of patients/total patients (%) PSA (ng/mL)				
	2.0–4.0	4.1–10.0	10.1–20.0	>20.1	Total
Standard sextant only	1/2 (50.0)	7/12 (58.3)	1/6 (16.7)	0/19 (0.0)	9/39 (23.1)
Lateral sextant only	0/2 (0.0)	1/12 (8.3)	2/6 (33.3)	0/19 (0.0)	3/39 (7.7)
Both sites	1/2 (50.0)	4/12 (33.3)	3/6 (50.0)	19/19 (100)	27/39 (69.2)

PSA, prostate specific antigen.

Self-administered questionnaire

A total of 118 (80.3%) and 116 (78.9%) men completed, respectively, the postbiopsy pain scale and the adverse events questionnaire. The 12-core biopsy procedure was reported as painful by 115 of the 118 patients (97.5%), despite the use of local anesthesia. Pain immediately after biopsy was reported as mild by 45 patients (39.1%), moderate by 43 patients (37.4%) and severe by 27 patients (23.5%). The mean overall pain score in these patients was 3.4 (range, 0–10). A gradual significant decrease in pain score was seen during the following 5 days ($P < 0.0001$, Fig. 2). Examining adverse events, hematuria, rectal bleeding, hematospermia or fever greater than 38°C after biopsy were experienced, respectively, in 107 (92.2%), 72 (62.1%), 10 (8.6%) and 3 (2.6%) men. Hematuria was graded mild in 52, moderate in 44 and severe in 11 patients. One patient needed hospitalization owing to clot retention. Rectal bleeding was graded mild in 42 patients, moderate in 24 patients and severe in 6 patients. Statistically significant decreases in the incidence of hematuria and rectal bleeding were noted during the 5-day period following biopsy ($P < 0.0001$, Table 5). Hematospermia was graded mild in 3, moderate in 3 and severe in 4 patients. No patient needed any medication for these morbidities.

Three patients experienced transient fever greater than 38°C, but recovered without hospitalization.

Discussion

Transrectal ultrasound-guided systematic sextant biopsy of the prostate gland has long been the standard procedure for detecting prostate cancer.[1] This procedure generally has minimal morbidity and is well tolerated by most patients and anesthesia is usually not required.[16] However, several studies have demonstrated sampling error rates of 17% to 30%.[2,5]

A number of studies have shown that alternative or more extensive prostate biopsy procedures may be more effective, with additional extensive sampling achieving 13% to 35% increases in cancer detection rates compared with standard sextant biopsy in Western series.[6,11] Terris *et al.* used a 12-core sampling strategy that included traditional sextant and lateral sextant sampling. They reported that 15% of the patients examined had cancer detected only by the lateral biopsy.[7] Levine *et al.* conducted two sets of simple sextant biopsies and reported a 30% increase in cancer detection.[8] Gore *et al.* reported that the detection rate of a 10-core biopsy procedure consisting of six lateral PZ cores plus mid-lobar base and apical sampling was higher (43.3%) than that of standard sextant biopsy (30.8%) and was identical to that of a 12-core biopsy (43.3%).[11]

Some investigators, however, have reported contrary findings. Naughton *et al.* prospectively randomized 244 patients to undergo 6- or 12-core biopsy.[9] The cancer detection rate of the 12-core biopsy (27%) was equivalent to that of the sextant biopsy (26%). In a Japanese population, Kojima *et al.* reported their experience with extensive 12-core sampling using a transperineal approach. Eighteen prostate cancers (13.8%) were

Table 4 Incidence of positive cores stratified by sextant sites and clinical findings

Clinical findings	% Cancer detection					
	Lateral sextant			Standard sextant		
	Apex	Mid	Base	Apex	Mid	Base
Overall	55.1	44.9	35.9	51.3	44.9	35.9
DRE						
Normal	41.2	29.4	20.6	26.5	17.6	17.6
Abnormal	65.9	56.8	47.7	70.5	65.9	50.0
US findings						
Negative	44.1	32.4	32.4	35.3	26.5	23.5
Positive	63.6	54.5	38.6	63.6	59.1	45.5
Prostatic volume (cm^3)						
≤40	58.1	45.2	32.3	51.6	43.5	33.9
>40	43.8	43.8	50.0	50.0	50.0	43.8
PSA (ng/mL)						
≤10	35.7	28.6	21.4	25.0	14.3	3.6
>10	66.0	54.0	44.0	66.0	62.0	54.0
PSAD ($ng/mL/cm^3$)						
≤0.15	0.0	25.0	50.0	25.0	0.0	0.0
>0.15	58.1	45.9	35.1	52.7	47.3	37.8

DRE, digital rectal examination; Mid, mid-prostate; PSA, prostate specific antigen; PSAD, prostate specific antigen density; US, ultrasonography.

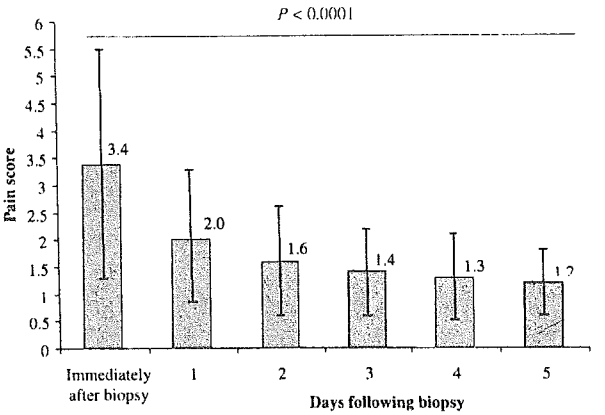

Fig. 2 Changes in pain score after 12-core transrectal ultrasound-guided biopsy during the 5-days following biopsy. The number represents mean pain score on scale bars. Error bars represent ±2 standard errors of the mean.

Table 5 Recovery trend of hematuria and rectal bleeding after 12-core transrectal ultrasound-guided biopsy during the 5-day postbiopsy period

	% patients with the finding (number of patients)				*P*-value
	Overall	Days			
		0–1	2–3	4–5	
Hematuria	92.2 (107/116)	91.4 (106/116)	73.0 (84/115)	46.4 (52/112)	<0.0001
Rectal bleeding	62.1 (72/116)	61.6 (69/112)	19.8 (22/111)	5.4 (6/111)	<0.0001

found outside the traditional sextant biopsy sites and would have been missed had the additional cores not been taken.[17] In the present study, we found only a 7.7% increase in cancer detection using an additional far lateral sextant biopsy in the PZ. This 12-core biopsy strategy would be potentially suitable in particular cohorts, such as PSA range 4.0–20.0 ng/mL (Table 3). Although the small sample size and the low number of events may have limited the statistical power for some of the analyses in this study, the 12-core biopsy scheme has yielded a 7.7% to 13.8% increase in cancer detection in Japanese series, which is much less than has been reported in Western series.

It still remains unclear, however, whether the increased cancer detection results simply from an increase in the number of cores or whether the choice of specific alternative locations is more important. We found cancer most frequently in cores at the apex level where the PZ, which has long been known to be susceptible to prostate carcinogenesis,[18] occupies the entire geometrical area. Apical cores can effectively sample the PZ, while cores taken at the mid-prostate to base level tend to sample the transition zone or the central zone, especially in cases of prostatic hypertrophy. It has also been shown previously that non-palpable prostate cancer predominantly occupies the anterior apex to mid-prostate region.[18] Thus, the cancer detection rate might have been much improved had we taken cores from anterior apical regions in the present study. All these considerations suggest that deep apical biopsy may provide an improved prostate cancer detection rate.[14]

Patient tolerance of the biopsy procedure itself is of great concern when an increased number of cores are called for, as is the associated morbidity. There are a number of possible explanations for failure of periprostatic local anesthesia to completely eliminate pain in the present series. The sensory nerve of the prostate gland is supplied mainly by fibers that originate from the caudal roots of S2 to S5 and the sympathetic chain of the presacral and hypogastric plexuses that emerge from the periprostatic neurovascular bundles located posterolateral to the prostate; that is, between the prostate and the rectum.[19,20] It is thus conceivable that our analgesic injections may have been placed too far away to effectively infuse the bundles, although the fact we carried out the procedure under direct transrectal ultrasonographic guidance renders this possibility somewhat unlikely. Another possibility is that the self-administrated questionnaire may not have provided the desired information. Since our questionnaire asked only about 'biopsy pain', patients may have taken this as a global term that included discomfort and/or anxiety. In addition, the questionnaire regarding pain on biopsy should carefully be appraised, since patients could easily have confused pain associated with biopsy with that associated with anesthetic injection. In this sense, our current approach should be regarded to assess pain in the whole biopsy procedure, including anesthesia. Our failure to explicitly cross-validate the questionnaire may be considered a limitation of the present study.

On the other hand, two randomized, double-blind, placebo-controlled studies have found that local anesthesia reduces, but does not completely eliminate, the pain of extensive core biopsy. Addla *et al.* compared 3-mL injections of 1% lidocaine at the basolateral neurovascular bundles plus a single injection at the apex with similar injections of placebo. The mean pain score was 3.0 in the 1% lidocaine group versus 4.3 in the control group.[21] Leibovici *et al.* similarly showed that the mean pain score of the overall procedure was significantly lower in their anesthesia group (3.06) than in the placebo group (4.15) and they injected patients bilaterally with 5 mL of either 1% lidocaine or 0.9% sodium chloride at the prostatic neurovascular bundles.[22]

The present study is limited, owing to its non-randomized design. Interestingly, however, the mean overall pain scores in the series by Leibovici *et al.* were similar to that in the current study (3.4). It seems most likely that local anesthesia may reduce pain associated with the biopsy to a significant degree, but is insufficient to completely block it.

In the present study, major morbidity, such as hematuria and rectal bleeding, subsided significantly during the 5-day period following biopsy. Naughton *et al.* also noted that there was no significant difference between the morbidity associated with 12-core biopsy and with standard sextant biopsy at an assessment 4 weeks after biopsy.[23]

Conclusions

We found cancer cores most frequently at the level of the apex, where the PZ is believed to occupy the entire region. Although the overall prostate cancer detection rate was not substantially enhanced by 12-core biopsy, this strategy was well tolerated and there was a gradual decrease in pain and morbidity over a relatively brief post-biopsy period. Further work is warranted to establish an optimal indication and biopsy strategy, including deep apical biopsy, and to investigate its associated morbidity in the Japanese male population.

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Appendix

Self-administered questionnaire during the 5-day post-biopsy period.

Question 1

Immediately after biopsy (Day 0)

Was the biopsy painful? How bad was the pain intensity? Please select figure from 0 (no pain) to 10 (the most serious).

5-day post-biopsy period (Day 1–5)

Do you have anal or perineal pain after biopsy? How bad is the pain intensity? Please select figure from 0 (no pain) to 10 (the most serious).

Question 2

During the 5-day postbiopsy period following biopsy (Day 1–5)

1 Do you notice any blood in your urine? How is it graded? Please select one from 0 (no event), 1 (mild), 2 (moderate) and 3 (severe).
2 Do you notice any rectal bleeding? How is it graded? Please select one from 0 (no event), 1 (mild), 2 (moderate) and 3 (severe).
3 Do you notice any blood in your semen? How is it graded? Please select one from 0 (no event), 1 (mild), 2 (moderate) and 3 (severe).
4 Do you have any fever? How high is it? Please select one from no fever, 37–38°C and >38°C.

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CANCER CORE DISTRIBUTION IN PATIENTS DIAGNOSED BY EXTENDED TRANSPERINEAL PROSTATE BIOPSY

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ABSTRACT

Objectives. To perform systemic 22-core transperineal ultrasound-guided template prostate biopsies in patients with previous negative transrectal ultrasound-guided prostate biopsy findings and evaluate the cancer core distribution.

Methods. Between April 2001 and December 2003, 128 men underwent systemic ultrasound-guided biopsy using the transperineal template technique. All patients had undergone at least one previous set of biopsies. Prostate biopsy was performed transperineally using an 18-gauge biopsy needle driven by a spring-loaded device. Four biopsies were obtained anterior to posterior from each of four coronal planes in the mid-region, and three biopsies were obtained anterior to posterior from each of two coronal planes in the apical region.

Results. Of the 128 patients, 29 (22.7%) had cancer according to an extended transperineal biopsy. Patients with prostate cancer had significantly greater prostate-specific antigen (PSA) levels (11.4 versus 7.6 ng/mL, $P = 0.0125$), smaller transition zone volumes (12.7 versus 21.2 cm^3, $P = 0.0012$), smaller prostate glands (31.5 versus 44.0 cm^3, $P = 0.0015$), and greater PSA density (0.36 versus 0.19 $ng/mL/cm^3$, $P < 0.0001$). The cancer core rates in the mid and apical parts of the anterior region (5.3% and 8.0%) were significantly greater than in the mid and apical parts of the posterior region (3.3% and 3.6%, $P = 0.0297$ and $P = 0.0132$, respectively).

Conclusions. The results of our study have shown that transperineal approaches are appropriate for sampling from the anterior half of the prostate gland. In patients in whom the diagnosis of prostate cancer is suspected, we believe that systemic 22-core transperineal ultrasound-guided template prostate biopsy might be the next optional diagnostic step after an initial negative prostate biopsy. UROLOGY **66**: 114–118, 2005. © 2005 Elsevier Inc.

Transrectal ultrasound (TRUS)-guided prostate biopsy is the standard method used in the diagnosis of prostate cancer. The use of prostate-specific antigen (PSA) measurement and digital rectal examination for prostate cancer screening has led to a dramatic increase in the number of TRUS-guided biopsies. Although TRUS-guided sextant biopsy provides safe and easy access to the prostate gland, this strategy may miss clinically significant cancer in 17% to 30% of patients.[1–3] Attempts to avoid these false-negative findings have led to numerous studies of alternative site sampling and extensive biopsy strategies, such as the 12-core biopsy or sextant biopsy plus two additional cores from the lateral peripheral zone.

We have previously shown that the primary extent of nonpalpable tumors appears to lie predominantly in the anterior half of the gland at the apex to mid-prostate level.[4] Thus, we suggested that additional biopsy cores taken from the more anterior half of the gland might enhance the detection of nonpalpable prostate cancer. Extensive ultrasound-guided transperineal biopsy has been reported to enhance the detection of prostate cancer in patients at high risk.[5] In one study, cancer was identified in the transition zone in 76% of the 38

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TABLE I. *Indications for extended transperineal biopsy*

Indication	Patients (n)
Persistent elevated PSA >2.1 ng/mL	115
Abnormal digital rectal examination, elevated PSA level	2
Prostatic intraepithelial neoplasia on previous biopsy	9
Atypia on previous biopsy	2

Key: PSA = prostate-specific antigen.

men with positive biopsy findings.[1] This strategy may be more appropriate for sampling the anterior half of the prostate gland. The purpose of this study was to clarify the enhancement of the cancer detection and examine the cancer core distribution in patients diagnosed using an extended 22-core transperineal prostate biopsy.

MATERIAL AND METHODS

Between April 2001 and December 2003, 128 men underwent systemic ultrasound-guided biopsy using the transperineal template technique. Patient age ranged from 37 to 85 years (median 67). All patients had undergone at least one or more previous sets of TRUS-guided biopsy. The median number of previous sets of TRUS-guided prostate biopsy and the median number of cores in sets of prior transperineal prostate biopsy was 1 and 6 (range 1 to 5 and 4 to 12, respectively). Table I lists the indications for repeat biopsy, including persistent elevated PSA level, abnormal digital rectal examination findings, and/or a history of prostatic intraepithelial neoplasia or atypia on previous biopsy. PSA was measured using the AxSYM PSA assay (Dinabot, Tokyo, Japan) and/or the Architect PSA assay (Dinabot). The results of these assays were not interconverted, because they are considered virtually identical.[4]

Patients were placed in the lithotomy position under spinal anesthesia. The prostate was localized in the transverse plane and then centered over the grid template overlay. The prostate volume was measured using an ultrasound machine (SSD 2000; Aloka, Tokyo, Japan) and the formula: height × width × length × 0.5236. Prostate biopsy was performed transperineally using an 18-gauge biopsy needle driven by a spring-loaded device. Four biopsies were obtained anterior to posterior from each of four coronal planes in the mid-region and three biopsies were obtained anterior to posterior from each of two coronal planes in the apical region (Fig. 1). All biopsy cores were separately labeled, fixed, and processed according to standardized and established protocols.[5]

The Mann-Whitney *U* test was used to assess the differences between the two groups. The chi-square test was used for the comparison of frequencies, with $P < 0.05$ considered significant. The statistical analyses were performed using the software StatView (Abacus Concepts, Berkeley, Calif).

RESULTS

Patient Characteristics and Cancer Detection According to Clinical Findings

Prostate cancer was detected in 29 (22.7%) of 128 patients, despite previous negative biopsies in this group (Table II). The median PSA level, transition zone volume, prostate gland volume, and PSA density was 10.4 ng/mL, 21.3 cm^3, 43.9 cm^3, and 0.25 ng/mL/cm^3, respectively. Patients with prostate cancer had significantly greater PSA levels (11.4 versus 7.6 ng/mL, $P = 0.0125$), smaller transition zone volumes (12.7 versus 21.2 cm^3, $P = 0.0012$), smaller prostate gland volumes (31.5 versus 44.0 cm^3, $P = 0.0015$), and greater PSA density (0.36 versus 0.19 ng/mL/cm^3, $P < 0.0001$) than those without cancer.

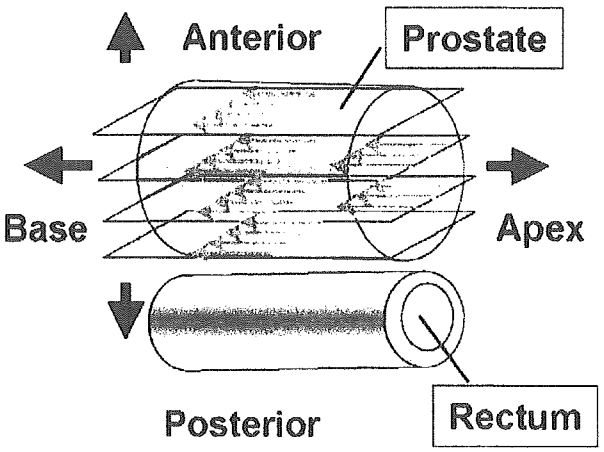

FIGURE 1. *Three-dimensional view of transperineal biopsy template.*

When the serum PSA level of the patients was stratified into six groups (2.1 to 4.0, 4.1 to 6.0, 6.1 to 8.0, 8.1 to 10.0, 10.1 to 20.0, and greater than 20.1 ng/mL), the group with a PSA level greater than 20.1 ng/mL had the greatest cancer detection rate (Table III). Although a tendency toward a greater cancer detection rate was found with a greater PSA level, no significant correlation between the cancer detection rate and serum PSA level was found ($P = 0.0506$).

Cancer Core Distribution

Figure 2 shows the number of cancer cores at each section on the template. In the apex area, the cancer core rate in the anterior region (number of cancer cores versus number of biopsy cores: 31 of 387, 8.0%) was significantly greater than that in the posterior region (14 of 387, 3.6%, $P = 0.0132$).

In the mid-prostate area, the cancer core rate in the anterior region (55 of 1032, 5.3%) was also significantly greater than in the posterior region (34 of 1032, 3.3%, $P = 0.0297$).

Overall, the cancer core rate in the anterior region (86 of 1419, 6.1%) was significantly greater than in the posterior region (48 of 1419, 3.4%, $P = 0.001$). Prostate cancer was detected throughout the prostate, but the greatest number of cancer cores was seen in the anterior area, especially the anterolateral region of the apex.

TABLE II. *Clinical characteristics*

	Patients (n)	Age (yr)	PSA (ng/mL)	TZ Volume (cm^3)	Prostate Volume (cm^3)	PSAD (ng/mL/cm^3)	Previous Set of Biopsies (n)	Previous Biopsy Cores Per Set (n)
Overall	128	67 (37–85)	10.4 (2.4–170)	21.3 (3.7–91.4)	43.9 (14.8–149.8)	0.25 (0.03–11.5)	1 (1–5)	6 (4–12)
Cancer	29	66 (53–85)	11.4 (2.4–170)	12.7 (3.7–55.7)	31.5 (14.8–85.4)	0.36 (0.03–11.5)	2 (1–4)	8 (4–12)
No cancer	99	67 (37–79)	7.6 (2.4–64)	21.2 (4.8–91.4)	44.0 (19.3–149.8)	0.19 (0.04–1.26)	1 (1–5)	6 (6–12)
P value	—	NS	0.0125	0.0012	0.0015	<0.0001	NS	—

Key: PSA = prostate-specific antigen; TZ = transition zone; PSAD = PSA density; NS = not significant.
Data presented as the median, with the range in parentheses.

TABLE III. *Incidence of positive cores stratified by serum PSA level*

PSA (ng/mL)	Patients (n)	Positive Patients (n)	Cancer Detected (%)
2.1–4.0	11	1	9.1
4.1–6.0	24	4	16.7
6.1–8.0	32	4	12.5
8.1–10.0	10	4	40
10.1–20.0	34	8	23.5
≥20.1	17	8	47.1
Total	128	29	22.7

Key: PSA = prostate-specific antigen.

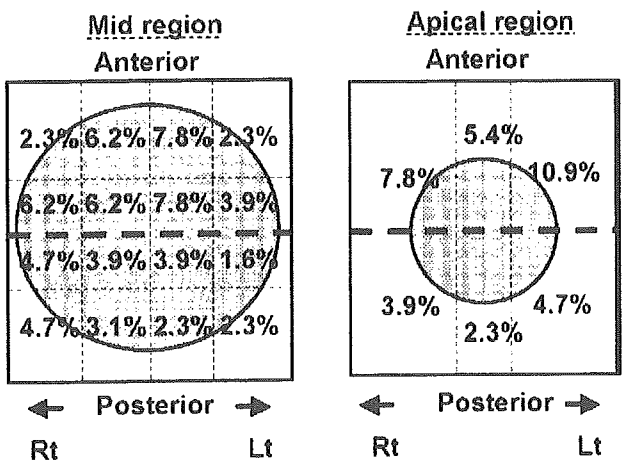

FIGURE 2. *Detection rate of prostate cancer in each core area of prostate.*

Correlation with Previous Sets of Transrectal Biopsies

The frequency of positive biopsy findings was compared between patient groups stratified by the number of previous TRUS-guided prostate biopsies. Of 70 patients with one previous transrectal biopsy set, prostate cancer was detected in 13 (18.6%). In the 58 patients with two or more previous transrectal biopsy sets, 16 (27.6%) had prostate cancer detected. No significant difference was found in the cancer-detection rate between the two groups. However, the serum PSA level was significantly greater in patients with two or more previous TRUS-guided biopsy sets than in patients with one previous set (11.5 versus 7.4 ng/mL, $P = 0.0094$). In addition, no difference in the median number of cores in prior transperineal prostate biopsy sets was found between the two groups (6.0 versus 8.0 per set, respectively).

Complications

The overall complication rate was 3.9%, with 5 patients having an adverse event. The most serious complication was acute prostatitis in 1 patient that required hospitalization for 10 days. Two men (1.6%) had urinary retention and two (1.6%) had difficult urination after transperineal biopsy.

COMMENT

Since its introduction by Hodge *et al.*,[8] systematic sextant transrectal biopsy of the prostate with TRUS guidance has been accepted as the standard technique for prostate cancer detection. However, the diagnostic characteristics of prostate cancer have changed since the introduction of PSA screening.

The false-negative rate of the sextant biopsy has been reported to be as much as 15% to 31%.[9–11] Lower cancer detection rates using sextant biopsy have been reported for a larger volume of prostatic tissue.[12,13] Attempts to avoid these false-negative findings have led to studies of alternative site sampling or extensive biopsy strategies that have demonstrated prostate cancer-detection rates greater than those of standard sextant biopsy.

We previously reported on the anterior distribution of nonpalpable tumors in radical prostatectomy specimens using a computer-assisted imaging technique.[1] The primary extent of nonpalpable tumors appeared to lie predominantly in the half of the gland at the apex to mid-prostate levels. On the basis of these results, we suggested that additional biopsy cores taken from more anterior regions of the gland might enhance the detection of nonpalpable cancer.

Extensive ultrasound-guided transperineal biopsy has been reported to enhance the detection of

prostate cancer in patients at high risk.[5] In one study, cancer was identified in the transition zone in 76% of the 38 men with positive biopsy findings.[5] This strategy may be more appropriate for sampling the anterior half of the prostate gland.

According to the present study, biopsy strategies that included cores obtained from the apical anterior region enhanced the detection rate of prostate cancer using extended transperineal prostate biopsy. Our results have demonstrated that the positive cancer core rate in the anterior area is significantly greater than the positive rate of the posterior area. The surprisingly high cancer detection rate for the anterolateral core emphasizes the importance of sampling from this region. These data were generated exclusively using template-guided transperineal approaches. Because the biopsy guide of the transperineal template directs the biopsy needle into the prostate at a more orthogonal angle, the prostatic anterior and apical regions are accessed and sampled more easily.

The optimal number of cores to take using this technique has not established. Shinghal and Terris[14] compared the results of TRUS-guided biopsies and transperineal ultrasound-guided (TPUS) sextant biopsies obtained from patients with known prostate cancer to evaluate the accuracy of TPUS prostate biopsy. TRUS-guided sextant biopsies detected 13 of the 20 tumors, and TPUS-guided biopsy detected only 2 of the 20 tumors. Thus, TRUS-guided and TPUS-guided sextant biopsies exhibited a sensitivity of 65% and 10%, respectively. The investigators concluded that TPUS-guided sextant biopsies are less accurate than TRUS-guided sextant biopsies in detecting prostate cancer. Kojima *et al.*[15] performed systemic 6-core and 12-core transperineal biopsy of the prostate in 138 and 541 consecutive patients according to digital rectal examination findings, TRUS findings, and/or increased serum PSA levels. The cancer detection rate was 18.8% for the 6-core and 24% for the 12-core biopsy. In addition, Emiliozzi *et al.*[16] reported on a randomized study of 6-core versus 12-core transperineal prostate biopsy, with a cancer detection rate of 38% and 51%, respectively. Taken together, the results of these studies suggest that the transperineal 6-core prostate biopsy is not the optimal number of cores for this technique.

The next question is when to recommend an extended 22-core transperineal prostate biopsy to patients after TRUS biopsies with negative findings. Our results have demonstrated that in patients with one previous TRUS biopsy set, prostate cancer was detected in 18.6%. In contrast, in patients with two or more previous biopsy sets, the cancer detection rate was 27.6%. A significant difference was not found in the positive rate according to the previous set of biopsy category. Patients with two or more previous biopsy sets included those patients with higher PSA levels. However, even in the high-risk group, TRUS prostate biopsy did not detect prostate cancer more than two times, and in one fourth of patients, prostate cancer was detected by extended transperineal prostate biopsy. According to these results, extended 22-core transperineal prostate biopsy might be acceptable as an optional method of repeat biopsy after initial negative TRUS sextant prostate biopsy, because TRUS biopsies might miss cancers in the anterior apical region. However, a possible disadvantage of increasing the number of biopsy cores is an increase in the incidence of detecting clinically insignificant prostate cancer. The spinal anesthetic requirement is also a disadvantage of this procedure. Additional studies are necessary to assess the value of an extended biopsy strategy in terms of oncologic outcome.

CONCLUSIONS

The results of our study have indicated that TRUS-guided biopsies might miss more cancer in the anterior region than in the posterior, especially in the anterolateral part of the apical region. Transperineal approaches could be appropriate for sampling from the anterior half of the prostate gland, and we believe that the systemic 22-core transperineal ultrasound-guided template prostate biopsy might be the next optional diagnostic step after a negative prostate biopsy in patients in whom the diagnosis of prostate cancer is suspected.

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