Comparison of 12- and 16-Core Prostate Biopsy in Japanese Patients with Serum Prostate-Specific Antigen Level of 4.0-20.0 ng/mL

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Purpose: In the present study, we compared 12- with 16-core biopsy in patients with prostate-specific antigen (PSA) levels of 4.0-20.0 ng/mL.

Materials and Methods: Between 2003 and 2010, 332 patients whose serum PSA level was between 4.0 and 20.0 ng/mL underwent initial transrectal ultrasound (TRUS)-guided needle biopsy. Of those patients, 195 underwent 12-core biopsy and 137 underwent 16-core biopsy.

Results: In the 12-core prostate biopsy group, 66 (33.8%) patients were found to have prostate cancer. On the other hand, in the 16-core prostate biopsy group of 137 patients, 61 (44.5%) were found to have prostate cancer. Among all patients, the prostate cancer detection rate was slightly higher in the 16-core biopsy group than in the 12-core biopsy group. Moreover, in patients with prostate volume > 30 mL or PSA density (PSAD) < 0.2, the prostate cancer detection rate was significantly higher in the 16-core biopsy group than in the 12-core biopsy group. There was no significant difference in pathological tumor grade, indolent cancer probability, or biopsy complication rate between the two groups.

Conclusion: In order to detect prostate cancer, 16-core prostate biopsy is safe and feasible for Japanese patients with serum PSA level of 4.0-20.0 ng/mL.

Keywords: prostate-specific antigen; prostatic neoplasms; sensitivity and specificity; biopsy; large-core needle; predictive value of tests.

INTRODUCTION

There were 679,000 new cases of prostate cancer worldwide in 2002, making it the fifth most common cancer in the world and the second most common cancer in men. Estimated age-standardized incidence rates were 119.9, 61.6 and 12.6 per 100,000 male population in the United States, Western Europe and Japan.[1] In Japan, despite the lower incidence of prostate cancer than in Western countries, diagnosis of the disease has been gradually increasing in recent years owing to widespread use of the serum prostate-specific antigen (PSA) test in Japanese men. For prostate cancer detection, Hodge and colleagues first proposed sextant systematic biopsy of the prostate under transrectal ultrasound (TRUS) in 1989.[2] Since then, many investigators have reported the usefulness of TRUS-guided systematic prostate biopsy. As originally described, 6 biopsies were obtained in the parasagittal line halfway between the lateral border and midline of the prostate on the left and right sides from the base, mid-gland and apex. Later, Stamey recommended shifting biopsies more laterally to better sample the anterior horn of the peripheral zone.[3]

Although TRUS-guided systematic prostate biopsy has been established as the standard, it is recognized that 6-core biopsy is inadequate for cancer detection. The standard sextant procedure misses 10% to 30% of cancers.[4,5] Recently, many investigators have indicated that extended prostate biopsy sampling with 8 or more cores might improve the prostate cancer detection rate.[6,7] In spite of the increased likelihood of prostate cancer detection by extended biopsy, the appropriate number of cores remains unclear. It is expected that increasing the number of biopsy cores would lead to improved cancer detection; however, the risk of detection of latent or insignificant prostate cancer may also be elevated. For accurate diagnosis with avoidance of overdiagnosis and overtreatment of latent cancer, a strategy for prostate cancer detection is important. In our study, we analyzed the data by comparing 12- with 16-core biopsy in patients with serum PSA level of 4.0-20.0 ng/mL. We evaluated extended 16-core prostate biopsy and defined the optimal number of biopsy cores.

MATERIALS AND METHODS

Between January 2003 and March 2010, 332 patients whose serum PSA concentration was between 4.0 and 20.0 ng/mL underwent initial transrectal ultrasound (TRUS)-guided needle biopsy at Yokohama City University Hospital and Yokohama City Medical Center. Between January 2003 and March 2005, 195 patients underwent 12-core biopsy (8 cores from the peripheral zone and 4 cores from the transition zone) at Yokohama City University Hospital, and between April 2005 and March 2010, 137 patients underwent 16-core biopsy (8 cores from the peripheral zone and 8 cores from the transition zone) at Yokohama City Medical Center, retrospectively. Sampling sites are shown in Figure 1. Patient characteristics of the 12- and 16-core biopsy groups are listed in Table 1. Serum PSA free/total ratio was significantly higher and patient age was significantly younger in the 16-core biopsy group than in the 12-core group.

All procedures were performed using diagnostic ultrasound machines, and core biopsies were obtained transperineally under ultrasound guidance, using a 18-gauge needle with a spring-loaded biopsy gun. All procedures were performed under local anesthesia (1% xylocaine). Before biopsy, all patients underwent TRUS and the prostate volume was measured. Total PSA as well as free PSA levels were determined with a DPC Imrise third generation PSA assay kit. Pathological tumor grade was classified according to the Japanese General Rules for Clinical and Pathological Studies on Prostate Cancer. Statistical analyses were performed by Mann-Whitney U test, chi-squared test, or logistic regression test using the statistical package for the social science (SPSS Inc, Chicago, Illinois, USA) version 17.0.

RESULTS

A total of 195 patients with serum PSA level ranging from 4.0 to 20.0 ng/mL underwent 12-core TRUS-guided prostate biopsy. Of those patients, 66 (33.8%) were found to have prostate cancer. On the other hand, a total of 137 patients with serum PSA level ranging from 4.0 to 20.0 ng/mL underwent 16-core TRUS-guided prostate biopsy. Of these 137 patients, 61 (44.5%) were found to have prostate cancer. Among all patients, the prostate cancer detection rate was slightly higher in the 16-core biopsy group than in the 12-core biopsy group, but the difference was not statistically significant ($P = .068$). Figure 2 shows positive core sites in 12- and 16-core biopsies. There were 15 cases (23.0%) of
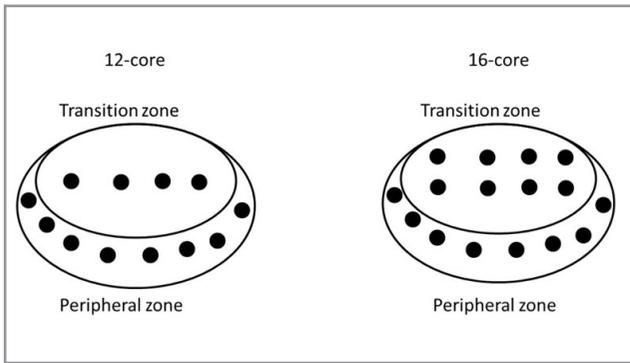
Figure 1. Sampling sites in 12- and 16-core prostate biopsy are shown.
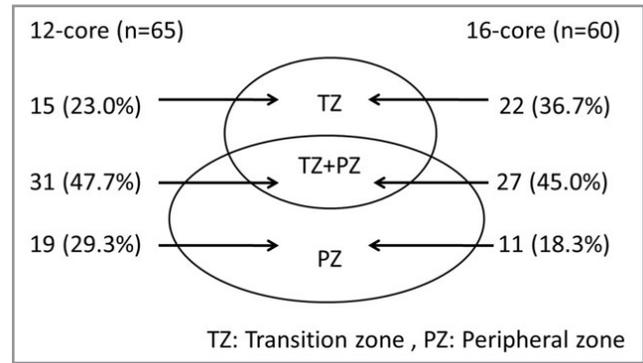
Figure 2. Positive core sites in 12- and 16-core biopsies are demonstrated (for explanation see text).

detection in transition zone (TZ) biopsy, 31 (47.7%) in the peripheral zone (PZ) and TZ, and 19 (29.3%) in PZ in the 12-core biopsy group. On the other hand, in the 16-core biopsy group, there were 22 cases (36.7%) of detection in TZ, 27 (45.0%) in PZ and TZ and 11 (18.3%) in PZ. There was no significant difference in positive core sites between the groups.

Among patients with prostate volume > 30 mL, 17 (15.5%) cancer patients were detected in the 12-core biopsy group and 25 (29.4%) in the 16-core biopsy group. Among patients with prostate volume > 30 mL, the prostate cancer detection rate was significantly higher in the 16-core biopsy group than in the 12-core biopsy group (P = .023).

Similarly, among patients with PSA density (PSAD) < 0.2, four cancer patients (6.3%) were detected in the 12-core biopsy group and 18 (34.0%) in the 16-core biopsy group. Among patients with PSAD < 0.2, the prostate cancer detection rate was significantly higher in the 16-core biopsy group than in the 12-core biopsy group (P < .0001).

We compared the pathological tumor grade obtained by 12-core biopsy with that obtained by 16-core biopsy. Median Gleason score of detected cancer was 7 [95% confidential interval (CI): 6.55-7.00] in the 12-core biopsy group and 7 (95% CI: 6.42-6.73) in the 16-core biopsy group. There was no significant difference in pathological tumor grade between the two groups (P = .083).

We predicted the possibility of insignificant prostate cancer in this study using Epstein criteria, and compared the insignificant cancer detection rate in the 12-core biopsy group with that in the 16-core biopsy group. Only one patient (0.5%) was detected as insignificant cancer in the 12-core biopsy group and 2 (1.5%) in the 16-core biopsy group. Our data showed that the insignificant cancer detection rate was not higher in the 16-core biopsy group than in the 12-core biopsy group (P = .31).

Significant independent variables for positive biopsies were age, prostatic-specific antigen level, prostate volume and VBR (volume biopsies ratio)[8] which means the prostate volume divided by the number of biopsies (P < .001). VBR had the strongest correlation coefficient out of all significant variables. We examined the predictive factors for prostate cancer patients with PSA of 4.0-20.0 ng/mL by multivariate analysis. Significant independent variables for positive biopsies were age, PSA, PSA F/T ratio, prostate volume, prostate TZ volume, PSAD and VBR. VBR had the strongest correlation coefficient out of all significant variables (Table 2). The detection rates for VBR of < 2.0, 2.0-2.9, 3.0-3.9 and > 4 were 68.0%, 34.1%, 20.0% and 7.7%, respectively.

The risks and complications of prostate cancer biopsy were compared between the 12-core and 16-core biopsy groups (Table 3). Adverse events were graded by National Cancer Institute Common Toxicity Criteria (NCI CTC) version 4.0. None of the patients in either group developed urinary tract infection. The occurrence rate of grade 3 hematuria and grade 2 urinary retention was similar in each group.

DISCUSSION

Although the optimum number of cores that should be ob-

Table 1. Patient characteristics of 12- and 16-core biopsy groups.

Variables	12-core	16-core	P
No. of patients	195	137	---
Age (years) (median, 95% CI)	69 (66.9-68.6)	67 (64.8-67.3)	.029
PSA (ng/mL) (median, 95% CI)	7.82 (8.34-9.42)	8.51 (8.65-10.15)	.234
PSA F/T ratio (median, 95% CI)	0.12 (.12-.14)	0.17 (.16-.19)	< .001
Prostate volume (mL) (median, 95% CI)	32.0 (33.1-38.1)	35.6 (35.6-43.2)	.192
TZ volume (mL) (median, 95% CI)	15.9 (16.2-19.3)	14.5 (16.4-21.5)	.708
PSA density (ng/mL/g) (median, 95% CI)	0.24 (.26-.31)	0.22 (.25-.32)	.575

Keys: PSA, prostate-specific antigen; F, free; T, total; TZ, transition zone.

tained at prostate biopsy remains unclear, many studies have shown that extended prostate biopsies are superior to sextant protocols for detecting prostate cancer.[9] In the present study, we compared the prostate cancer detection rate and clinicopathological findings in the 12-core biopsy group and 16-core biopsy group. The total detection rate of prostate cancer in patients with PSA of 4.0-20.0 ng/mL was 66 of 195 patients (33.8%) in the 12-core biopsy group. These results were similar to those in previous reports.[10,11] In the 16-core biopsy group, the prostate cancer detection rate was 61 of 137 patients (44.5%), which was superior to that in the 12-core biopsy group although the difference was not statistically significant. Among the patients with prostate volume > 30 mL, 17 (15.5%) cancer patients were detected in the 12-core biopsy group and 25 (29.4%) in the 16-core biopsy group. Among patients with prostate volume > 30 mL, the prostate cancer detection rate was significantly higher in the 16-core biopsy group than in the 12-core biopsy group (P = .023). Similarly, among patients with PSAD < 0.2, four

cancer patients (6.3%) were detected in the 12-core biopsy group and 18 (34.0%) in the 16-core biopsy group. Among patients with PSA density < 0.2, the prostate cancer detection rate was significantly higher in the 16-core biopsy group than in the 12-core biopsy group (P < .0001). Our results indicate that 12-core prostate biopsy might be inadequate in patients with large prostate volume or low PSAD. In patients with prostate volume > 30 mL or PSAD < 0.2, 16-core biopsy improved the prostate cancer detection rate over that with 12-core biopsy.

Various efforts to improve prostate cancer detection have been reported such as increasing the number of cores, laterally focused biopsy, changing access, biopsy corresponding to diffusion-weighted magnetic resonance images before biopsy or saturation biopsy using a template.[12-14] The second consideration is the location of cores. From repeat prostate biopsy studies, it emerges that prostate cancer tends to locate more frequently in the lateral and anterior apical regions than in the transition zone.[15,16]

Although it is not surprising that taking more cores enhances the cancer detection rate and diagnostic ability, the possibility of increasing the detection of clinically insignificant cancer should be considered. A lower threshold for serum PSA and extended biopsy might lead to a marked increase in detection of small, low-grade prostate cancers.[17,18] In an attempt to identify clinically insignificant prostate cancer, Epstein and colleagues examined preoperative clinical and pathological features in 157 men with clinical stage T1c prostate cancer who underwent radical prostatectomy, to find features that could predict insignificant tumors (organ-confined tumors less than 0.2 mL, pathological Gleason sum

Table 2. Predictive value for cancer detection in patients with serum PSA levels of 4-20 ng/mL.

Variables	P	Exp (B)
Age	.066	1.043
PSA	.409	1.076
PSA F/T ratio	.068	0.011
Prostate volume	.070	1.074
TZ volume	.120	0.945
PSA density	.659	2.762
VBR	.002	0.264

Keys: PSA, prostate-specific antigen; F, free; T, total; TZ, transition zone. Exp(B) = This is the exponentiation of the B coefficient, which is an odds ratio.

Table 3. Comparison of complication grades between 12-core and 16-core biopsy.

Variables	12-core (n = 75)	16-core (n = 126)	P
Urinary retention (G2)	7 (6.55-7.00)	7 (6.42-6.73)	.546
Hematuria (G3)	7 (6.55-7.00)	7 (6.42-6.73)	.996

6 or lower).[19] Their model for predicting an insignificant tumor was no Gleason grade of 4 or 5 in the biopsy specimen and either [1] PSAD of 0.1 ng/mL per gram or less, two or one biopsy cores involved with cancer (minimum of six cores obtained) and no core with more than 50% involvement or [2] PSAD ≤ 0.15 ng/mL per gram and cancer smaller than 3 mm in only one prostate biopsy sample (minimum of six cores). This model had a positive predictive value of 95% and a negative predictive value of 66% in their own dataset. These investigators predicted that 73% of their cases were insignificant tumors. We predicted the possibility of insignificant prostate cancer in this study using Epstein criteria,[19] and compared the insignificant cancer detection rate in the 12-core biopsy group with that in the 16-core biopsy group. Our data showed that the insignificant cancer detection rate was not higher in the 16-core biopsy group than in the 12-core biopsy group. There was no evidence that 16-core biopsy elevated clinically insignificant cancer detection. Pepe and colleagues[20] reported that prostate cancer diagnosed by saturation biopsy with a median of 30 cores showed a significant cancer in 48/22 (87.3%) patients. Only 12.7% of cases showed insignificant cancer, but the detection rate of more aggressive disease with a risk of non-organ-confined cancer in their series was 27.3%. Epstein and colleagues reported that overall, only 7/274 (2.6%) men had an "insignificant" tumor in the prostatectomy specimen, and a model including Gleason grade, PSAD, and number of positive biopsy cores did not provide an accurate means of selecting patients for active monitoring in their patient cohort.[21]

The risks and complications of prostate cancer biopsy were compared in the 12-core and 16-core biopsy groups. None of the patients developed urinary tract infection. The occurrence rate of grade 3 hematuria and grade 2 urinary retention was similar in each group. These results were consistent with previous reports.[22,23]

There are some limitations about this study. In particular, it is a major weakness that this study is retrospective. For obtain the optimum number of cores, prospective randomized clinical trial may be warranted

CONCLUSION

We concluded that 16-core prostate biopsy is safe and feasible for Japanese patients with serum PSA level of 4.0-20.0 ng/mL. Further studies in different population with greater sample size are needed to draw final conclusion.

ACKNOWELDGEMENT

CONFLICT OF INTEREST

None declared.

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