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Transrectal Ultrasound-guided 10-core Biopsy of the Prostate for Japanese Patients

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ABSTRACT

To determine the utility of transrectal ultrasound (TRUS)-guided 10-core prostate biopsy (sextant plus 4 far lateral cores) for Japanese patients, we compared it with the standard sextant for detection of prostate cancer. The study patients were 564 consecutive Japanese men (median age 71 years) who underwent 10-core biopsy because of PSA values of ≥ 2.0 ng/ml at Hiroshima University Hospital between March 2000 and December 2004. The overall cancer detection rate for the 10-core biopsy was 42.6% (240/564), which was significantly higher than the 36.3% (205/564) for the standard sextant biopsy (P=0.0330), with a 14.6% (35/240) improvement. The 10-core biopsy also detected a significant number of additional cancers in the subgroups of patients with PSA values of 2~10 ng/ml (P=0.0275), a prostate volume of > 20 cc (P=0.0440), or normal findings of digital rectal examination (P=0.0304). The 10-core biopsy scheme detected 9.6% and 2.1~8.3% more cancers than the lateral sextant (apex, lateral mid portion, and lateral base) and the probable different combinations of 8-core biopsy designs, respectively. Compared to the standard sextant biopsy, the 10-core biopsy did not detect an increased proportion of clinically insignificant cancers. There was no severe morbidity, and only 2 patients (0.4%) were briefly hospitalized due to high fever. These results show that the TRUS-guided 10-core biopsy yields a better prostate cancer detection rate than the 6-core or 8-core protocol without severe complications. Therefore, it seems to be practicable for Japanese patients.

Key words: *Prostate cancer, Biopsy, Japanese, PSA*

Systematic sextant biopsy of the prostate under transrectal ultrasound (TRUS) guidance was introduced in 1989 and has revolutionized our ability to diagnose prostate cancer[8]. For over a decade, sextant biopsies have been considered the gold standard for diagnosis of prostate cancer. However, limitations in cancer detection, including a high false-negative biopsy rate, have led to changes in biopsy techniques[15]. Recently, several groups have evaluated more extensive systematic sampling of the lateral aspects of the peripheral zone to improve cancer detection rates[3,6]. To date, however, a biopsy strategy that is optimal in terms of such aspects as the most appropriate number and location of cores remains to be established.

In the present study, we investigated the usefulness and morbidities of the TRUS-guided extended 10-core biopsy scheme for Japanese patients.

MATERIALS AND METHODS

A total of 564 consecutive Japanese patients who underwent TRUS-guided 10-core biopsy at Hiroshima University Hospital between March 2000 and December 2004 were enrolled in the study. The indications for the biopsy included a PSA level of 2.0 ng/ml or higher by automated chemiluminescent immunoassay (ACS) assay, irrespective of the findings of digital rectal examination (DRE). Patients who had previously undergone prostate biopsy were excluded from the

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study. Anticoagulation or aspirin therapy was discontinued beforehand. Antibiotic prophylaxis with a new oral quinolone was started on the morning of the biopsy and continued for 3 days. All participants read and signed an informed consent form.

The biopsy procedures were as follows. With the patient in the lithotomy position, transrectal ultrasonography was performed with an Aloka SSD-2000 ultrasound device and a 7-MHz probe. The prostate was imaged in the transverse and sagittal planes, and the prostate volume was measured by a non-planimetric ellipsoid method. Subsequently, under local periprostatic or intraprostatic anesthesia[11], standard sextant biopsies were obtained in the midlobar parasagittal plane, halfway between the lateral edge and midline of the prostate gland on the right and left sides from the apex, mid gland and base, and directed as much towards the periphery of the prostate as possible at the apex. As well as the sextant cores, four additional far-lateral biopsies were performed by positioning the probe just medial to the lateral edge of the prostate at the mid and basal portions of the gland bilaterally according to the method of Presti et al[14]. Biopsies were further obtained from any suspicious areas such as hypoechoic regions, if present. The 10 core sites are illustrated in Fig. 1. All procedures were performed by two of the authors (K.M. and H.Y.) on an outpatient basis using 18-gauge core biopsy needles, which obtained a biopsy trough measuring 17 mm with an automatic, spring-loaded device.

Whenever the final pathological diagnoses were available, we calculated cancer positivity rates for each portion of the 10 cores and compared them among different combinations of the 10 areas. We also compared cancer detection rates between the standard sextant and the extended 10-core biopsy designs according to various clinical parameters. In addition, clinicopathological features of the patients whose cancers were found by the additional lateral biopsies among the 10 cores were evaluated. All biopsy specimens were examined and reviewed by a single pathologist (Y.T.) according to the Gleason grading system[4]. The clinical stage for each cancer patient was determined according to the General Rules for Clinical and Pathological Studies on Prostate Cancer (3rd edition)[9]. Stages B, C and D were defined as confinement of the tumor to within the prostate, extension of the tumor through the prostate capsule or invasion to the seminal vesicle, and tumor with metastasis, respectively[9]. Morbidities associated with the biopsy were assessed by interview at various times during the 4 weeks following the biopsy.

Statistical analyses were conducted by the Mann-Whitney U test or the chi-squared test using the 'JMP' software package (ver. 5.1.2). The level of statistical significance was set at $p < 0.05$.

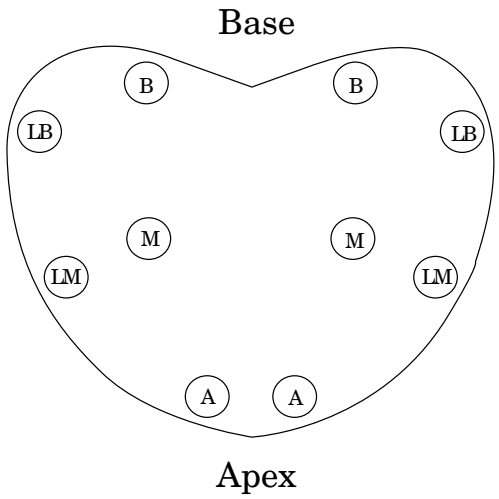

Fig. 1. Schematic representation of 10-core biopsy sites.
A: Apex, M: Mid gland, B: Base, LM: Far lateral mid gland, LB: Far lateral base.

RESULTS

The basic characteristics of the 564 patients are shown in Table 1. 240 and 321 patients were found to be positive and negative for prostate cancer by the 10-core biopsy protocol, respectively. The remaining 3 patients were diagnosed as having prostate cancer exclusively by lesion-directed biopsies, and therefore regarded as having shown a negative biopsy result. In comparison with the patients who had a negative biopsy result, those with a positive result were significantly older, and had a higher PSA value, a smaller prostate volume and a greater PSA density (PSAD).

Cancer detection rates were compared between the standard sextant and the extended 10-core (sextant plus 4 lateral peripheral) biopsy strategies. Of the 564 patients, 205 (36.3%) and 240 (42.6%) were diagnosed as having prostate cancer by the sextant and the 10-core biopsy schemes, respectively. Thus the 10-core biopsy design increased the cancer detection rate significantly by 14.6% (35/240) for the cancer patients as a whole (p=0.0330). Cancer detection rates for different subgroups of patients were further compared between the two strategies, and are summarized in Table 2. For patients with PSA values of 2.0~10 ng/ml, the 10-core method detected 22.0% (28/127) more cancers, which was significantly better than the rate for the standard sextant (p=0.0275). Meanwhile, for patients with PSA values greater than 10 ng/ml, there was no significant difference in the rate of cancer detection between the two methods. Similarly, compared with the sextant procedure, the 10-core

Table 1. Basic characteristics of patients

	Results of 10-core biopsy§		Overall	p Value (Positive vs. Negative) (Mann-Whitney U test)
	Positive	Negative		
No. of patients	240	324	564	
Age (y)	45~84	41~84	41~84	0.0008
Median	71.8	69.6	70.5	
PSA† value (ng/ml)	2.1~296	2.0~86.0	2.1~296	< .0001
Median	9.6	4.7	6.5	
Prostate volume (cc)	9.2~112	7.1~157	7.1~157	< .0001
Median	26.0	31.4	28.9	
PSAD‡ (ng/ml/cc)	0.07~13.4	0.04~2.86	0.04~13.4	< .0001
Median	0.40	0.16	0.21	

† Prostate-specific antigen
‡ PSA density
§ Positive and negative results were defined as detection and non-detection of prostate cancer by the 10-core biopsy, respectively.

Table 2. Cancer detection rates in different patient subgroups: comparison between sextant and 10-core biopsy

	Total	10-core (%)	Sextant (%)	Increase (%)	p value (chi-squared)
Overall	564	240 (42.6)	205 (36.3)	35 (14.6)	0.0330
PSA value (ng/ml)					
2.0~10.0	395	127 (32.2)	99 (25.1)	28 (22.0)	0.0275
10.1~20.0	76	36 (47.4)	33 (43.4)	3 (8.3)	0.6250
> 20	93	77 (82.8)	73 (78.5)	4 (5.2)	0.4579
Prostate volume (cc)					
≤ 20	111	65 (58.6)	59 (53.2)	6 (9.2)	0.4174
> 20	453	175 (38.6)	146 (32.2)	29 (16.6)	0.0440
PSAD (ng/ml/cc)					
≤ 0.15	192	37 (19.3)	27 (14.1)	10 (27.0)	0.1709
> 0.15	372	203 (54.6)	178 (47.8)	25 (12.3)	0.0667
Age (y)					
≤ 70	245	88 (35.9)	75 (30.6)	13 (14.8)	0.2126
> 70	319	152 (47.6)	130 (40.8)	22 (14.5)	0.0795
DRE†					
Normal	442	156 (35.3)	126 (28.5)	30 (19.2)	0.0304
Abnormal	122	84 (68.9)	79 (64.8)	5 (6.0)	0.4967
TRUS‡					
Normal	444	148 (33.3)	122 (27.5)	26 (17.6)	0.0579
Abnormal	120	92 (76.7)	83 (69.2)	9 (9.8)	0.1911
PSA value 2.0~10.0 ng/ml					
+ Prostate volume (cc)					
≤ 20	74	33 (44.6)	27 (36.5)	6 (18.2)	0.3151
> 20	321	94 (29.3)	72 (22.4)	22 (23.4)	0.0474
+ PSAD (ng/ml/cc)					
≤ 0.15	183	34 (18.6)	25 (13.7)	9 (26.5)	0.2008
> 0.15	212	93 (43.9)	74 (34.9)	19 (20.4)	0.0590
+ Age (y)					
≤ 70	183	47 (25.7)	36 (19.7)	11 (23.4)	0.1697
> 70	212	80 (37.7)	63 (29.7)	17 (21.3)	0.0808
+ DRE					
Normal	341	103 (30.2)	78 (22.9)	25 (24.3)	0.0302
Abnormal	54	24 (44.4)	21 (38.9)	3 (12.5)	0.5582
+ TRUS					
Normal	339	94 (27.7)	73 (21.8)	21 (22.3)	0.0612
Abnormal	56	33 (58.9)	26 (46.4)	7 (21.2)	0.1852

† Digital rectal examination ‡ Transrectal ultrasonography

method increased the cancer detection rate significantly for patients with a prostate volume > 20 cc or normal DRE, whereas it yielded no significant increase for those with a prostate volume ≤ 20 cc or abnormal DRE. For the subgroups of patients stratified by PSAD, age or TRUS, there was no significant increase in the number of additional cancers detected by the 10-core biopsy strategy. Because the effect of increasing the number of cores was marked in patients with PSA values of 2~10 ng/ml, these patients were further stratified and analyzed in a similar manner. Consequently, the 10-core biopsy again detected a significant number of additional cancers in the subgroups of patients with a prostate volume of > 20 cc (p=0.0474) or normal findings of DRE (p=0.0302). However, for the subgroups of patients stratified by PSAD, age or TRUS, no significant increase was noted in the number of additional cancers detected by the 10-core biopsy strategy.

The clinicopathological features of the 35 patients whose prostate cancers were diagnosed by the additional lateral cores were then evaluated. As shown in Table 3, no significant difference was noted between these patients and those who were diagnosed by the conventional mid-lobar sextant biopsies in terms of clinical stage distribution and Gleason score. The number of patients with clinically insignificant cancer was estimated to be 2 (5.7%) out of the 35 according to the Epstein criteria for insignificant prostate cancer as assessed on biopsy (PSAD < 0.15 ng/ml/cc, Gleason score ≤ 6, fewer than 3 cores containing prostate carcinoma, and ≤ 50% involvement of any core with prostate carcinoma)[2]. The corresponding figure was 14 out of 205 (6.8%) for patients who were diagnosed by mid-lobar sextant biopsies, with no significant difference between the two groups.

Table 4 shows the site-specific percentage cancer detection data for the 240 patients who were positive. Of the 5 biopsy regions, the apex had the highest cancer detection rate, followed in order by the lateral mid and mid portions, the lateral base and the base. There was a significant difference in the cancer detection rate between the apex and the base (p=0.0003). We then determined the site-specific unique percentage cancer detection rates, and found that 20 (8.3%) of the 240 positive patients were diagnosed solely from the apex. These figures implied that if apical biopsies had been omitted, 8.3% of the cancers would have been missed. The corresponding percentages for the mid gland and the base were 12/240 (5.0%) and 5/240 (2.1%), respectively. If we had performed 8-core biopsy with the conventional sextant and 2 lateral-mid cores, we would thus have missed 9/240 (3.8%) of the total cancers. This figure would have been 16/240 (6.7%) with the use of an 8-core biopsy design including the sextant and 2 lateral base cores. The percentage cancer detection rate for the lateral sextant (apex, lateral mid, and lateral base) was 90.4% (217/240), which was higher than the 85.4% (205/240) for the conventional sextant.

Among the morbidities associated with the 10-core biopsy design, hematuria, hematochezia, hematospermia, or fever exceeding 38˚C were noted in 123 (21.8%), 4 (0.7%), 5 (0.9%) and 11 (2.0%) patients, respectively. Two patients (0.4%) were hospitalized for a few days due to high fever.

Table 4. Site-specific overall and unique percentage cancer detection rates for 240 patients with prostate cancer

	Overall (%)	Unique† (%)
Conventional sextant	205 (85.4)	53 (22.1)
Apex	151 (62.9)	20 (8.3)
Mid gland	139 (57.9)	12 (5.0)
Base	112 (46.7)	5 (2.1)
Additional far lateral	187 (77.9)	35 (14.6)
Lateral mid gland	147 (61.3)	16 (6.7)
Lateral base	132 (55.0)	9 (3.8)

† Proportion of patients who were diagnosed solely from the portions of interest.

Table 3. Clinicopathological features of patients diagnosed exclusively by additional lateral biopsies: comparison with those of cancer patients diagnosed by conventional mid-lobar sextant biopsies

	Additional Lateral	Mid-lobar Sextant	p Value
No. of patients	35	205	
Clinical stage			0.1125
B	32 (91%)	155 (76%)	
C	1 (3%)	20 (10%)	
D	2 (6%)	30 (14%)	
Gleason score			0.2021
≤ 6	18 (51%)	74 (36%)	
7	12 (35%)	84 (41%)	
≥ 8	5 (14%)	47 (23%)	
Insignificant cancer†	2 (5.7%)	14 (6.8%)	0.8069

† According to the Epstein criteria as assessed on biopsy (PSAD < 0.15 ng/ml/cc, Gleason score ≤ 6, fewer than 3 cores containing prostate carcinoma, and ≤ 50% involvement of any core with prostate carcinoma.)

DISCUSSION

The detection of prostate cancer relies on the ability to adequately sample the areas most likely to harbor the cancer. The goal of any prostate biopsy regimen is to detect as many cancers as possible using the fewest biopsies. In this context, it is very clear that mid-lobar sextant biopsies, as described by Hodge et al[8], are no longer the gold standard, because a number of recent studies have demonstrated that the standard sextant biopsy fails to detect cancers, especially in the lateral and anterior regions[5]. As a solution, Stamey recommended shifting biopsies more laterally in order to better sample the anterior horn of the peripheral zone from where the majority of cancers arise[16]. Most recently, sampling the apex has also been regarded as important because the anterior horns of the peripheral zone extend not only laterally but also apically[18,19]. Increasing the number of cores also seems to be effective, because several investigators have reported 15–35% improvements in prostate cancer detection rates in Western series as a result of taking 8[13,14], 10[3,7], 11[1], 12[17], and 13[6] core biopsies compared with the standard sextant biopsy. However, there are also some contradictory reports, which claim that extensive multicore biopsy procedures do not enhance cancer detection[12].

In the present study involving Japanese patients with PSA levels of 2.0 ng/ml or greater, the cancer detection rate for the 10-core biopsy technique was as high as 42.6%, and significantly greater than the figure of 36.3% for the conventional sextant procedure (p=0.0330). The extent of the increase was 14.6%, which was similar to the figure of 15–25% reported in Western series[7,13,14]. These results clearly indicate that for Japanese men also, the 10-core biopsy regimen is more advantageous for cancer detection than the conventional sextant protocol.

This was especially evident for patients with PSA values of 10 ng/ml or lower. While the 10-core biopsy technique did not significantly increase the cancer detection rate for patients with PSA levels higher than 10 ng/ml, it enhanced the cancer detection rate significantly by 22% for those with PSA values of 10 ng/ml or less (p=0.0275). Our 10-core biopsy technique also significantly enhanced the cancer detection rate for the subgroup of patients with a larger prostate volume (> 20 cc) or normal findings of DRE, as previous studies have also reported[7,14]. Thus, the extended 10-core biopsy protocol was superior to the conventional 6-core strategy especially for patients with PSA levels below 10 ng/ml, a prostate volume exceeding 20 cc, or normal findings of DRE.

With regard to the optimal placement of cores, our study revealed that the apex had the highest rate of cancer detection. This was consistent with a previous report on transrectal 12-core biopsy for Japanese men by Matsumoto et al, in which cancer positivity was found most frequently in cores taken at the apex[10]. Our data also confirmed that a lateral sextant regimen (apex, lateral mid gland and lateral base) detected more cancers than the standard sextant protocol (apex, mid gland and base). This was probably because our lateral and apical biopsies extensively sampled the peripheral zone, which extends laterally and peripherally, occupying the entire geometric area of the apex, and is the site in the prostate most frequently affected by cancer[18,19]. In contrast, our data showed that base biopsy had the lowest detection rate. The incidence of cancer may be low in the peripheral zone at the level of the base. Thus our results indicate the importance of directing the needles toward the peripheral border of the prostate in the lateral sextant regimen of the 10-core biopsy to increase the likelihood of cancer detection.

With respect to the number of cores, analysis of the site-specific cancer detection rate demonstrated that the 10-core biopsy detected 9.6% more cancers than the lateral sextant procedure. Also, the 10-core biopsy strategy detected 2.1~8.3% more cancers than all the probable different combinations of the 8-core biopsy protocol. Although the differences were not significant, this implies that even an 8-core biopsy would have missed 5–20 cases of cancer. Thus, our findings indicate that at least a 10-core biopsy is desirable in order to avoid overlooking cancer.

There are two major areas of concern about the 10-core biopsy: the possibility of increasing the number of insignificant cancers detected, and the morbidities associated with the procedure. The insignificant cancers are those that do not pose a threat to life even without treatment[2]. If the 10-core biopsy increases the number of insignificant cancers detected, we cannot but conclude that the clinical significance of increasing the number of cores is low. However, among the cancers that were detected by additional lateral biopsies, the proportion of clinically insignificant cancers did not differ from that of cancers detected by the standard sextant biopsy (5.7% and 6.8%, p=0.8069), although the estimation was based on biopsy findings, and not on actual excised specimens. In addition, Western series have reported that the majority of prostate cancers diagnosed by extensive multicore biopsy procedures were clinically significant[7,14]. With regard to morbidities, out of the total of 564 patients who underwent the procedure, only 2 (0.4%) required hospitalization for a few days due to high fever, and all morbidities responded to conservative management. The incidence of complications requiring hospitalization was comparable with the 0.7~0.9% reported in Western series[7,13]. Moreover, Naughton et al[12]

found that extended multicore biopsy did not increase the incidence of fever or hospitalization compared with standard sextant biopsy. The morbidity rates of hematuria, hematochezia and hematospermia in our study were rather lower than those reported for 6-core biopsy[12]. Therefore we do not consider that this technique increases the risk of morbidities.

In conclusion, the present study is the first to assess the benefit of TRUS-guided 10-core prostate biopsy for Japanese patients. Our results show that this procedure gives a better prostate cancer detection rate than the 6-core or 8-core protocol without significantly severe complications. Therefore we consider it an excellent strategy, and recommend further study to determine whether it can be applied as a gold standard for the diagnosis of prostate cancer.

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