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Insulin-like Growth Factor-binding Protein-3 Gene -202 *A/C* Polymorphism Is Correlated with Advanced Disease Status in Prostate Cancer[1]

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ABSTRACT

The circulating level of insulin-like growth factor-binding protein-3 (IGFBP-3) is inversely associated with the risk of prostate cancer (PCa) and its progression and may be modulated by the *A/C* polymorphism at position -202 in the promoter region of *IGFBP-3*. This study was conducted to evaluate the role of the *A/C* polymorphism as a genetic modifier in the etiology of PCa and its disease status. The polymorphism was analyzed by a PCR restriction fragment-length polymorphism technique in 307 PCa patients, 221 benign prostatic hyperplasia (BPH) patients, and 227 male controls. No significant difference in the genotype frequency was found between the PCa or BPH patients and controls (PCa *versus* control, $P = 0.316$; BPH *versus* control, $P = 0.964$). Regarding the tumor stage, the *C* allele was more frequently observed in patients having tumors with higher stage (P for trend = 0.002). When the PCa patients with localized disease (stage A + B + C) were considered as reference, those with *CC* and *AC* genotype had a significantly increased risk of metastatic disease (stage D) compared with those with *AA* genotype [age-adjusted odds ratio (aOR) = 3.89, 95% confidence interval (CI) = 1.42–10.64, $P = 0.008$, and aOR = 1.68, 95% CI = 1.01–2.79, $P = 0.044$, respectively]. The presence of the *C* allele appeared to be associated with an increased risk of metastatic PCa with a gene dosage effect (aOR = 1.82, 95% CI = 1.23–2.68, $P = 0.002$). Similarly, significant findings were also observed when PCa patients were compared between those with organ-confined disease (stage A + B) and those with extra-prostatic extension (stage C + D). Furthermore, the *C* allele was present more frequently in patients with higher tumor grade. In conclusion, the *IGFBP-3* -202 *A/C* polymorphism was not associated with susceptibility to PCa and BPH in Japanese men, but the presence of the *C* allele may cumulatively increase the risk for tumor metastasis and for having tumors with a biologically more aggressive phenotype. Because of the significant differences in incidence of clinically evident PCa according to racial backgrounds, the conjecture should be further examined in different racial populations.

INTRODUCTION

The incidence of PCa[4] has been rapidly increasing during the last decade in East Asia (1). However, the incidence rates remain significantly higher in African-Americans or in American Caucasians than Japanese (2–4). Although Japanese immigrants in the United States have experienced a marked increase in PCa incidence, the incidence is less than half of that of American Caucasians (3, 4). These epidemiological studies suggested that the occurrence of PCa is influenced by the multitude of genetic and environmental factors.

Deregulation of the IGF system was suggested to be specifically implicated in PCa. IGFBP-3, which is a major circulating IGFBP (5), binds to IGF-I, forming a complex that limits the IGF-I bioavailability for binding to the IGF-I receptor (6). IGFBP-3 suppressed the mitogenic and antiapoptotic action of IGF-I (7, 8) and was inversely associated with malignant transformation of the prostate (9, 10) and the progression of PCa (11–14). Studies have revealed that the circulating IGF-I and IGFBP-3 levels may be altered in PCa patients. In these patients, the circulating IGF-I level was shown to be often increased (15, 16), whereas the circulating or prostate tissue levels of IGFBP-3 were often decreased (9–11, 15, 17–19). Moreover, a series of studies have demonstrated that the plasma IGFBP-3 levels were significantly lower in African-American men than those in American Caucasian men and the highest in Japanese men (20–22). Because the lower IGFBP-3 levels could result in a greater IGF-I bioavailability (5), these findings may partly explain why the African-American men have a greater incidence of PCa than the American Caucasian and Japanese men.

A recent Physicians' Health Study revealed the presence of *A/C* polymorphism at position -202 in the promoter region of *IGFBP-3* and reported that the polymorphism was correlated with the circulating IGFBP-3 level in men and circulating IGFBP-3 levels were higher when the subjects possessed at least one *A* allele (23). They suggested that the circulating IGFBP-3 level may be modulated by the *A/C* polymorphism. To assess the role of the *A/C* polymorphism as a genetic modifier in the etiology of PCa and its disease progression, we investigated the *IGFBP-3* genotype distribution in men with or without PCa and in PCa patients with or without metastatic disease.

MATERIALS AND METHODS

Subjects. We studied a consecutive series of 800 subjects, including 307 PCa patients, 221 BPH patients, and 272 male controls at the Akita University Medical Center and its related community hospitals in Akita prefecture, who agreed to participate in this study. Most subjects were enrolled in previous studies (24–26). The subjects were selected between April 1997 and November 2001 for the PCa patients, between August 1997 and November 2000 for the BPH patients, and between March 1998 and September 2001 for the male controls.

All PCa patients were diagnosed histologically with specimens obtained from transrectal needle biopsy or transurethral resection of the prostate for voiding symptoms. The clinical or pathological stage of PCa at the time of diagnosis was determined by reviewing the medical records based on the Tumor-Node-Metastasis system (27). PCa was classified into stage A ($T_{1a-b}N_0M_0$), stage B ($T_{1c-2}N_0M_0$), Stage C ($T_{3-4}N_0M_0$), and Stage *D* ($T_{1-4}N_1M_{0-1}$ or $T_{1-4}N_{0-1}M_1$) by the modified Whitmore-Jewett system (28). In 120 cases in whom radical prostatectomy was performed, final pathological stage was applied, and in other 187 cases without radical prostatectomy, clinical stage was applied. Pathological grading of PCa was determined according to the General Rule for Clinical and Pathological Studies on Prostate Cancer by the Japanese Urological Association and the Japanese Society of Pathology (29), which is based on the WHO criteria (30) and according to the Gleason score (31). All pathological grading was based on needle biopsy specimens in stage B–D patients and surgical specimens in stage A patients. Well-, moderately, and poorly differentiated carcinoma generally correspond to Gleason scores of 2–4, 5–7, and 8–10, respectively (29, 32). In the present study, because the two grading systems were individually used by local

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[4] The abbreviations used are: PCa, prostate cancer; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen; aOR, adjusted odds ratio; CI, confidence interval.

pathologists, the tumor grade system was newly categorized as follows: (*a*) the low-grade cancer included the well-differentiated or Gleason 2–4 carcinomas; (*b*) the intermediate grade cancer included the moderately differentiated or Gleason 5–7 carcinomas; and (*c*) the high-grade cancer included the poorly differentiated or Gleason 8–10 carcinomas. In 3 patients, the final pathological grade was not determined because the endometrioid carcinoma, whose grading system has not been established, was pathologically diagnosed.

All BPH patients had various degrees of lower urinary tract symptoms and an apparent prostatic enlargement by digital rectal examination. The serum total PSA levels were measured in all of the patients, and men with an elevated total PSA level (4 ng/ml or greater by the Tandem-R assay; Hybritech, Inc., San Diego, CA) were confirmed not to have PCa by transrectal sextant biopsies. Serum total PSA was measured using the Tandem-R assay in most cases. When serum total PSA was measured using kits other than the Tandem-R, the measured total PSA level was adjusted to that of the Tandem-R assay using a formula published elsewhere (33). The male controls, comprising 272 volunteers without any apparent voiding symptoms, were selected randomly from a natural Japanese population attending a medical check-up. They were all tested for serum total PSA levels (the Tandem-R assay), and those with abnormal total PSA levels (≥4 ng/ml, the Tandem-R assay) were omitted from the normal controls. Written informed consent was obtained from all of the control subjects. The present study was approved by the Institutional Review Board of the Akita University School of Medicine.

PCR Restriction Fragment-length Polymorphism Analysis. DNA was extracted from blood samples collected from all subjects using a QIAamp Blood Kit (Qiagen, Hilden, Germany) or by the standard method with proteinase K digestion followed by phenol/chloroform extraction. The 244-bp fragment encompassing the *A* to *C* polymorphic site in the *IGFBP-3* promoter region was amplified using specific primers 5′-CCGAGAGCGGAAGGGG-TAAG-3′ in sense and 5′-TGCTCAGGGCGAAGCACGGG-3′ in antisense. PCR reactions were carried out in a 25-μl volume containing ~20 ng of genomic DNA, 1 × PCR buffer supplied by a manufacturer, 0.2 mM each deoxynucleotide triphosphate (dATP, dCTP, dGTP, and dTTP), 1 mM $MgCl_2$, 50 pmol of each primer, and 1 unit of Ampli-Taq Gold DNA polymerase (Perkin-Elmer, Branchburg, NJ). After a 10-min initial denaturation step at 95°C, 35 cycles of PCR reaction consisting of 95°C for 30 s, 55°C for 30 s, and 72°C for 60 s were carried out, followed by a 7-min final extension step at 72°C in a thermal cycler (GeneAmp PCR System 9700; Perkin-Elmer). After confirmation of successful PCR amplification by 1.5% agarose gel electrophoresis, each PCR product was digested overnight with 5 units of *FspI* enzyme at 37°C (New England Biolabs, Inc., Beverly, MA) and was electrophoresed on 2.5% agarose gel.

The 244-bp PCR fragment was divided into 164- and 80-bp fragments when the *FspI* site was present. The genotype was designated as *C* or *A* when the *FspI* restriction site was present or absent, respectively (Fig. 1*A*). The validity of the PCR restriction fragment-length polymorphism analysis was confirmed by direct sequencing of several PCR samples with each genotype using the BigDye FN Sequencing kit (PE Applied Biosystems, Foster City, CA; Fig. 1*B*).

Statistical Analysis. χ^2 test for Hardy-Weinberg equilibrium was evaluated in each group (PCa, BPH, and control; degrees of freedom = 1). Pearson's χ^2 test was used to compare allele frequencies and genotype frequencies. The OR and 95% CI with respect to *IGFBP-3* genotypes were calculated from a multivariate logistic regression model. We hypothesized the *C* allele as an inherent genetic risk factor for PCa and its disease progression. Statistical modeling was performed on the relative risk of the *CC* or *AC* genotype against the *AA* genotype independently using the model adjusted by age as a potential confounding factor (in years). The relation between genotype distributions with tumor grade or stage was also examined using a multivariate logistic regression analysis adjusted by age as a potential confounding factor. The Cochran-Armitage trend test was used to examine the relation between the allele frequency and increasing tumor stage or grade. In addition, the gene dosage effect of the *C* allele was assessed by modeling a linear effect on the log odds scale for each *C* allele in a multivariate logistic regression, such as the genotypes *CC*, *AC*, *AA*, which were valued as "2," "1," and "0," respectively. The mean age of the subjects among the three groups was examined using the unpaired two-tailed *t* test. All data were entered into an access database and analyzed using the Excel 2000 and SPSS (version 10.0J; SPSS, Inc.) software.

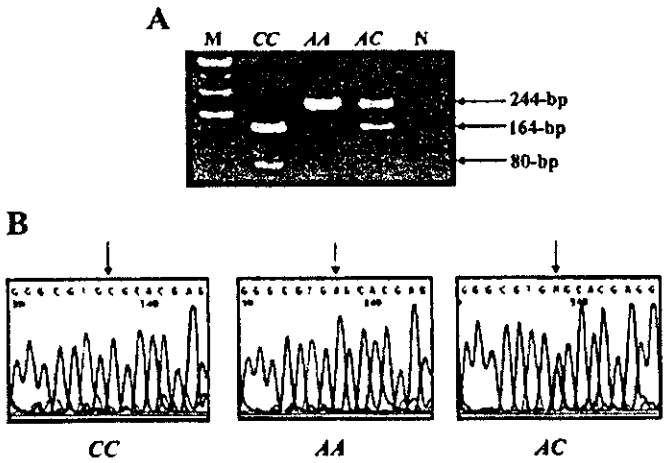

Fig. 1. Representative screening for the *IGFBP* genotypes. *A*, patterns for each of the genotypes *CC*, *AA*, and *AC* (*Lanes 2–4*) screened by PCR restriction fragment-length polymorphism analysis. *Numbers in parentheses* are the size of each fragment (*bp*). *M*, molecular size marker (*Lane 1*). *N*, negative control (*Lane 5*). *B*, results of nucleotide sequence analysis for each of the genotypes. *Arrows*, the location of nucleotides at which the polymorphism occurs.

RESULTS

Subject Characteristics. The mean age (±SD) was 71.77 ± 7.96 years for the PCa patients, 70.94 ± 9.43 years for the BPH patients, and 70.79 ± 8.06 years for the controls. No significant differences in the mean age were found between the PCa patients and controls ($P = 0.143$) or between the BPH patients and controls ($P = 0.853$). There were 27 stage A patients whose PCa was diagnosed incidentally by specimens removed for BPH treatment. Eighty-six PCa patients had clinical stage D2 disease, and 9 had clinical D1 disease, which was judged by radiological studies, whereas 15 patients were pathologically confirmed as having lymph node metastatic (D1) disease. In total, 110 patients were classified into having metastatic PCa; 106 and 64 PCas were classified into stage B and C disease, respectively, by clinical or pathological findings (Table 1).

Genotypes of *IGFBP-3* -202 *A/C* Polymorphism and Risk of PCa and BPH. The frequencies of the *IGFBP-3* genotype in the PCa, BPH, and control groups are shown in Table 1. No significant differences in the allele frequencies were found when the PCa patients (*A* 0.78, *C* 0.22) and BPH patients (*A* 0.75, *C* 0.25) were compared with the controls (*A* 0.75, *C* 0.25), respectively. The allele frequencies of the controls were significantly different from those of the American men reported by the Physicians' Health Study (*A* 0.4, *C* 0.6; $P < 0.001$; Ref. 23). The *IGFBP-3* genotype frequency in each group (PCa, BPH, and control) was in Hardy-Weinberg equilibrium ($P > 0.05$, data not shown).

Statistical analyses of the genotype prevalence showed that no significant differences were found between the PCa patients and controls ($P = 0.316$), between the BPH patients and controls ($P = 0.964$), and between the PCa patients and BPH patients ($P = 0.482$), respectively (Table 1). To evaluate the risk of PCa and BPH according to the *IGFBP-3* genotypes, the logistic regression analysis was conducted with adjustment for age at the time of diagnosis (Table 1). Compared with the men with the *AA* genotype, no significant increased risk of PCa and BPH was found in men with the *AC* or *CC* genotype (Table 1).

***IGFBP-3* Genotype and PCa Disease Status.** We examined the relation between the *IGFBP-3* -202 *A/C* polymorphism and tumor stage or grade at the time of diagnosis. Regarding the tumor stage, the frequency of the *AA* genotype decreased as the tumor stage increased. The *C* allele was more frequently observed in patients having tumors

Table 1 *IGFBP-3 genotype frequencies in PCa patients, BPH patients, and control males*

Study group	Total no.	Genotype (%)			C allele frequency (%)
		AA	*AC*	*CC*	
PCa[a]	307	189 (61.6)	100 (32.6)	18 (5.9)	22.1
Stage[b]					
A	27	20 (74.1)	6 (22.2)	1 (3.7)	14.8
B	106	70 (66.0)	35 (33.0)	1 (0.9)	17.5
C	64	42 (65.6)	17 (26.6)	5 (7.8)	21.1
D	110	57 (51.8)	42 (38.2)	11 (10.0)	29.1
Grade[c]					
Low	45	29 (64.4)	15 (33.3)	1 (2.2)	18.9
Intermediate	142	89 (62.7)	45 (31.7)	8 (5.6)	21.5
High	117	68 (58.1)	40 (34.2)	9 (7.7)	24.8
BPH[d]	221	125 (56.6)	83 (37.6)	13 (5.9)	24.7
Control (reference)	272	152 (55.9)	105 (38.6)	15 (5.5)	29.7

[a] PCa *versus* control, $P = 0.316$ by χ^2 test.
[b] According to the Whitmore-Jewett system. Stage A = $T_{1a-b}N_0M_0$, Stage B = $T_{1c-2}N_0M_0$, Stage C = $T_{3-4}N_0M_0$ and Stage D = $T_{1-4}N_1M_{0-1}$ or $T_{1-4}N_{0-1}M_1$. *C* allele frequency, $P = 0.002$ by the Cochran-Armitage trend test. Stage A + B + C *versus* Stage D, $P = 0.010$ by χ^2 test. Stage A + B *versus* Stage C + D, $P = 0.010$ by χ^2 test.
[c] Low grade = well-differentiated carcinoma (WHO) or Gleason score 2–4 carcinoma, Intermediate grade = moderately differentiated carcinoma (WHO) or Gleason score 5–7 carcinoma, High grade = poorly differentiated carcinoma (WHO) or Gleason score 8–10 carcinoma. *C* allele frequency, $P = 0.215$ by the Cochran-Armitage trend test.
[d] BPH *versus* control, $P = 0.964$ by χ^2 test.

with higher stage (P for trend = 0.002; Table 1). A significant difference in the genotype frequency was found between the localized PCa patients (stage A + B + C) and metastatic PCa patients (stage D; $P = 0.01$) and the organ-confined PCa patients (stage A + B) and extraprostatic PCa patients ($P = 0.01$; Table 1). Compared with the *AA* genotype, the PCa patients with *CC* genotype had a 3.89-fold increased risk of metastatic disease, and those with the *AC* genotype had a 1.68-fold increased risk of metastatic disease (Table 2). When the *CC*, *AC*, and *AA* genotypes were valued as "2," "1," and "0" into the model, respectively, the presence of the *C* allele significantly increased the risk of metastatic disease with a gene dosage effect (aOR = 1.82, 95% CI = 1.23–2.68, $P = 0.002$). However, when the patients with localized and metastatic PCa were independently compared with the normal controls, no significant risk of localized PCa (aOR = 0.54, 95% CI = 0.23–1.38, $P = 0.198$) or metastatic PCa (aOR = 1.95, 95% CI = 0.85–4.5, $P = 0.118$) was found in men with the *CC* genotype against those with the *AA* genotype. Similar findings were found when the PCa patients were compared between those with organ-confined (stage A–B) disease and those with extraprostatic extension (stage C–D; Tables 1 and 2).

No significant difference in the genotype frequency was found among the three subgroups of grade (low, intermediate, and high grade; $P = 0.715$; Table 1). The frequency of *AA* genotype was decreased, whereas that of *CC* genotype was increased as the tumor grade rose (Table 1). Although not statistically significant by the linear trend test, the *C* allele was more frequently observed in patients with higher tumor grade (P for trend = 0.215; Table 1).

DISCUSSION

A relatively small number of studies concerning the *IGFBP-3* -202 *A/C* polymorphism on common diseases has been reported, and the genotype frequency of this polymorphism in the normal population has not been fully clarified. The present study revealed that the *A* allele appeared to be significantly more common in the Japanese men (*A* 0.75, *C* 0.25) than American men (*A* 0.4, *C* 0.6) reported by the Physicians' Health Study (23). It was reported previously that the *A* allele was correlated with a higher plasma level of IGFBP-3 in men (23) and that the mean plasma IGFBP-3 level was significantly higher in Japanese men than that in African-American and American Caucasian men (21). We found no association between the *IGFBP-3* genotype and susceptibility to PCa or BPH in Japanese men. However, it should be noted that, because the control subjects were a cohort of aged men with normal PSA levels and no significant voiding symptoms, it is possible that the control subjects might include substantial cases with BPH and some PCa cases as well.

The present findings showed a significant association between the *IGFBP-3* -202 *A/C* polymorphism and risk of advanced disease in PCa patients. Furthermore, the presence of the *C* allele appeared to increase the risk with a gene dosage effect. However, the conjecture should be interpreted with a caution because the frequency of the *CC* genotype was relatively low in Japanese men, leaving the possibility that such significant findings were caused by chance. In addition, there was no significant difference in the *IGFBP-3* genotype frequency between the metastatic PCa patients and normal controls, and the effect of the *C* allele was not evident when compared with the normal controls. However, if the IGHBP-3 system as influenced by the *IGHBP-3* genotype was genuinely involved in PCa progression but not in its early carcinogenesis, and if the *C* allele had a deteriorating effect, whereas the *A* allele had a protective effect in its progression, it would be reasonable that the *IGHBP-3* allelic frequency was associated with disease status but not distinct between normal and PCa subjects. It remains to be verified if the effect of the *C* allele (or the *A* allele) was only biologically significant under a certain condition in PCa patients.

Table 2 *aOR according to IGFBP-3 genotype*

		aOR (95% CI, P) according to IGFBP-3 genotype[a]		
		AA	*AC*	*CC*
Study group				
	PCa against control	1.00	0.77 (0.55–1.09, 0.144)	0.97 (0.48–2.00, 0.942)
	BPH against control	1.00	0.96 (0.66–1.40, 0.840)	1.06 (0.48–2.30, 0.892)
Tumor stage[b]				
	Stage D against Stage A + B + D	1.00	1.68 (1.01–2.79, 0.044)	3.89 (1.42–10.6, 0.008)
	Stage D + C against Stage A + B	1.00	1.31 (0.80–2.15, 0.279)	7.82 (1.74–35.2, 0.007)
Tumor grade[b]				
	High against low + intermediate	1.00	1.16 (0.70–1.91, 0.567)	1.84 (0.69–4.90, 0.221)

[a] These data were adjusted for age.
[b] Tumor stage and grade systems are the same as Table 1.

Smith *et al.* (34) hypothesized that IGFBP-3 is directly involved in generating osteoblastic bony metastases, perhaps via a PSA-dependent paracrine loop involving both the PCa and bone cells. A recent large-scaled study has demonstrated that a lower plasma IGFBP-3 level was associated with a significantly higher risk of advanced-stage PCa (13). Kanety *et al.* (11) suggested that a lower level of serum IGFBP-3 was detected in PCa patients with metastatic disease compared with healthy controls. Furthermore, the preoperative plasma IGFBP-3 level has been shown to be a useful predictor of treatment failure after radical prostatectomy (14). Miyata *et al.* (35) recently also mentioned that the serum IGFBP-3:PSA ratio might be a useful prognostic marker of advanced PCa in Japanese PCa patients, and a lower level of plasma IGFBP-3 might be correlated with the presence of the *C* allele with a gene dosage effect (23). These findings may support our present finding that the presence of the *C* allele was significantly associated with an increased risk of metastatic disease in PCa patients with a gene dosage effect. On the other hand, Wolk *et al.* (16) found no association between the serum IGFBP-3 levels and disease status of PCa. However, the age, energy intake, nutrient status, and body mass index of individuals can profoundly affect the circulating IGFBP-3 level, and the hormones, growth factors, and cytokines are related to the *IGFBP-3* mRNA expression (8). The presence of prostatic disease, especially PCa, may alter the circulating IGFBP-3 level and other IGF-related protein, therefore making the interpretation of results of retrospective case control studies more difficult. Furthermore, the levels and activity of IGF-I and IGFBP-3 in the prostate cells appear to be more complicated (36). Additional studies on the biological role of the *IGFBP-3* -202 *A/C* polymorphism in the context of the IGF-I and IGFBP-3 axis should take many confounding factors into account.

The promoter region, where the *IGFBP-3* -202 *A/C* polymorphism is located, may harbor the response elements for various hormone receptors and transcription factors, including insulin, growth hormone, retinoic acid, vitamin D, estrogen, thyroid hormone, glucocorticoids, tumor necrosis factor-α and β, and epidermal growth factor (8, 37). As shown by an *in vitro* expression assay (23), the *IGFBP-3* mRNA synthesis may be altered in correlation with the presence of the *C* or *A* allele, which might have a significant impact on the disease status in PCa patients.

In conclusion, the *IGFBP-3* -202 *A/C* polymorphism was not associated with the susceptibility to PCa and BPH in Japanese men. However, the presence of *C* allele may be a genetic risk factor for metastasis or advanced disease status in PCa patients with a gene dosage effect and may also be associated with a biologically more aggressive tumor. However, the results should be interpreted with caution because of the relatively small number of study subjects and absence of significant difference in the genotype frequency between the metastatic PCa patients and normal controls. The proposed biological mechanism for the role of *A/C* polymorphism in progression of PCa will require further exploration and validation.

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Original Article

Morbidity of laparoscopic radical prostatectomy: Summary of early multi-institutional experience in Japan

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Abstract

Aim: Laparoscopic radical prostatectomy is being evaluated throughout the world. The aim of the present study is to report early multi-institutional experience of the procedure in Japan.

Methods: A total of 148 men who were diagnosed with clinically localized prostate cancer underwent laparoscopic radical prostatectomy at seven different institutions in Japan. Early complications (within 30 days postoperatively) and postoperative convalescence were reviewed retrospectively. The median age of patients was 68.0 years (range, 51–80).

Results: The median operative time was 403 minutes (range, 167–925; average, 427). Blood loss ranged from 50 to 5000 mL (median, 540; average, 856). A total of 66 complications were reported in 55 patients (37.2%). Intraoperative complications were noted in 25 of 148 patients (16.9%): 10 rectal injuries (6.8%); five bladder injuries (3.4%); five cases of subcutaneous emphysema (3.4%); two intestinal injuries (1.4%); one major vessel injury (0.7%); one ureteral injury (0.7%); and one obturator nerve injury (0.7%). Overall, 16 of 148 patients (10.8%) required open conversion or postoperative open surgical repair. The most common postoperative complications were anastomotic leakage (6.8%), wound-related complications (4.7%) and perineal pain (4.7%). The bladder catheter was removed on day 7 or earlier in 73 cases (49.3%). The median time to ambulation was 1 day (mean 1.4, range 1–5). Oral intake was started on postoperative day 1 in 67 patients (45.2%) and on postoperative day 2 in 65 (43.9%).

Conclusion: Although laparoscopic radical prostatectomy is technically demanding, reduced blood loss and shorter convalescence periods can be expected from the procedure. Surgeons should be aware of the disturbingly high morbidity rate related to early experience. By mastering laparoscopic skills and sharing knowledge, surgeons could reduce the impact of the learning curve required to complete this procedure competently.

Key words laparoscopic radical prostatectomy, laparoscopy, morbidity, prostate cancer.

Introduction

From the time that the French groups introduced laparoscopic radical prostatectomy, the procedure has been evaluated worldwide.[1–9] With increasing experience and technical improvement, they have been successful in decreasing the incidence of morbidity associated with

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the procedure.[4,6,8,9] However, before accepting this procedure as a part of our standard care, particularly in comparison with retropubic or perineal radical prostatectomy, many questions need to be answered in terms of morbidity, functional results, oncological outcome and cost. The aim of the present study is to report early multi-institutional experience in Japan, focusing mainly on morbidity and postoperative related to the procedure. The detailed early oncological outcome has been reported elsewhere.[10]

Methods

Between December 1999 and September 2001, 148 men diagnosed with clinically localized prostate cancer (T1–T3N0M0) underwent laparoscopic radical prostatectomy at seven different institutions in Japan. The median age of patients was 68.0 years (range, 51–80). Written informed consent was obtained from all patients. According to the 1997 TNM classification,[11] the 148 patients were classified as follows: stage T1 (82 patients); T2 (59 patients); and T3 (7 patients). Twenty-five patients underwent neoadjuvant endocrine therapy, with or without chemotherapy (antiandrogen therapy alone; or luteinizing hormone-releasing hormone agonist, with or without futraful) for a median period of 3 months (range, 0.5–10 months). Median preoperative serum prostate-specific antigen (PSA) was 7.7 ng/mL (range, 1–269 ng/mL). PSA was measured at different laboratories using various techniques. These included Tandem R PSA assay (YAMASA, Chiba, Japan); ECLIA assay (Nippon Roche KK, Tokyo, Japan); DPC Immulize PSA assay (Dia-Iatron, Tokyo, Japan); Architect PSA assay (Dinabot, Tokyo, Japan); AxSYM PSA assay (Dinabot, Tokyo, Japan); and Lumipulse PSA assay (Fujirebio, Tokyo, Japan). Results of these assays were not inter-converted, because they are considered virtually identical.[12]

Several different surgeons conducted laparoscopic radical prostatectomy at each institution according to the original method of the Montsouris[4] and Heilbronn group,[13] or with some modifications.[14] Transperitoneal approach was performed in 96 patients, extraperitoneal approach in 21, and the remaining 21 procedures were completed with combined approaches as reported elsewhere.[14] Eighty-five patients underwent simultaneous laparoscopic pelvic lymph node dissection at the discretion of each surgeon. A nerve-sparing procedure was performed in 33 patients (22.3%). Bilateral techniques were performed in eight and unilateral nerve-sparing in 25. Low-dose heparin was used as a prophylactic measure for thromboembolic complications in 30 patients.

An electronic database was created, and the data were abstracted directly from the records. Data abstracted and entered were specifics of surgery, such as duration, blood loss, transfusion, nerve-sparing methods, early complications, open conversion and postoperative convalescence (duration of bladder catheterization, time to first oral intake and time to ambulance). Early complications were defined as those that occurred within 30 days postoperatively. Mann–Whitney *U*- and Kruskal–Wallis tests were used to compare variables, and χ^2 statistics were used to compare categorical variables, with $P \leq 0.05$ as significant.

Results

Duration of surgery, blood loss and transfusion

The median operative time was 403 minutes (range, 167–925; average, 427). Blood loss ranged from 50 to 5000 mL (median, 540; average, 856). Of 148 patients, 103 (69.6%) had blood loss of 1000 mL or less. Only nine patients (6%) received allogeneic transfusion. None of the 51 patients who donated preoperative autologous blood received subsequent allogeneic transfusion. There was no difference in operative time or blood loss between patients with and without neoadjuvant hormonal therapy (data not shown).

Intraoperative complications and open conversion

A total of 66 complications was reported in 55 patients (37.2%) (Table 1). Intraoperative complications were noted in 25 of 148 patients (16.9%): 10 rectal injuries (6.8%); five bladder injuries (3.4%); five cases of subcutaneous emphysema (3.4%); two intestinal injuries (1.4%); one major vessel injury (0.7%); one ureteral injury (0.7%); and one obturator nerve injury (0.7%). Three of the 10 rectal injuries were repaired laparoscopically. Four required open conversion, two of which involved the creation of a temporary colostomy. In the remaining three patients, rectal injury was not identified during surgery, but was diagnosed postoperatively in the context of the postoperative peritonitis or ileus. These patients required temporary intestinal diversion by colostomy. Although there was no significant difference, patients who were treated with neoadjuvant hormone therapy experienced a higher incidence of rectal injury (12%) than those who did not receive such treatment (5.7%). Two ileocolonic injuries required open conversion. Other open conversions were conducted as

Table 1 Morbidity of 148 patients who underwent laparoscopic radical prostatectomy for clinically localized prostate cancer

Complication	No. pts (%)
Intraoperative	
Rectal injury	10 (6.8)
Bladder injury	5 (3.4)
Subcutaneous emphysema	5 (3.4)
Intestinal injury	2 (1.4)
Major vessel injury	1 (0.7)
Obturator nerve injury	1 (0.7)
Ureteral injury	1 (0.7)
Postoperative	
Anastomotic leakage	10 (6.8)
Wound infection/dehiscence	7 (4.7)
Perineal pain	7 (4.7)
Ileus	3 (2)
Peritonitis	2 (1.4)
Lymphocele	2 (1.4)
Port site herniation	2 (1.4)
Vesicorectal fistula	2 (1.4)
Catheter malfunction	1 (0.7)
Hydronephrosis	1 (0.7)
Pelvic hematoma	1 (0.7)
Acute cholecystitis	1 (0.7)
Peripheral nerve palsy	1 (0.7)
Hoarseness	1 (0.7)
Death within 30 days	0 (0)

Table 2 Postoperative convalescence of 148 patients who underwent laparoscopic radical prostatectomy for clinically localized prostate cancer

	No. pts (%)
Days catheterized	
3	4 (2.7)
4	7 (4.7)
5	27 (18.2)
6	16 (10.8)
7	19 (12.8)
8	12 (8.1)
9	5 (3.4)
10	2 (1.4)
> 10	56 (37.8)
Days to ambulance	
1	106 (71.6)
2	30 (20.3)
3	7 (4.7)
4	4 (2.7)
5	1 (0.7)
Days to first oral intake	
1	67 (45.3)
2	65 (43.9)
3	6 (4.1)
4	3 (2.0)
5	2 (1.4)
> 5	4 (2.7)

a result of massive bleeding in two patients, long duration of surgery in two, technical difficulty of urethroanastomosis in two, and obesity in one. Thus, overall, 16 of 148 patients (10.8%) required open conversion or postoperative open surgical repair.

Postoperative early complications

Distribution of the types of early complications is shown in Table 1. The most common complications were anastomotic leakage (6.8%), wound-related complications (4.7%) and perineal pain (4.7%). All but one wound-related complication were easily managed in a conservative method. There were two cases of lymphocele that were managed conservatively. One involved the tube malfunction of a retained catheter. Two patients developed vesicorectal fistula that required colostomy. One patient had postoperative unilateral hydronephrosis that resolved spontaneously. One patient had formation of pelvic hematoma that did not require drainage.

Gastrointestinal complications consisted of three intestinal obstructions, one case of peritonitis, and one of acute inflammation of the gall bladder. The peritonitis was caused by intraoperative rectal injury, which was later diagnosed and required colostomy. Two patients had port site herniation. One had peripheral nerve palsy due to the long duration of surgery. There were no thromboembolic complications such as pulmonary embolism or deep venous thrombosis. There were no cases of myocardial infarction. No patients died perioperatively.

Postoperative convalescence

The median duration of bladder catheterization was 7 days (mean, 14.4; range 3–196). The bladder catheter was removed on day 7 or earlier in 73 cases (49.3%). The median time to ambulation was 1 day (mean, 1.4; range, 1–5). One hundred and five patients (70.9%) were able to walk on postoperative day 1. The median duration to first oral intake was 2 days (mean, 2.6; range, 1–120). Oral intake was started on postoperative day 1 in 67 patients (45.2%) and on day 2 in 65 (43.9%). Oral intake was delayed in the remaining patients due to bowel complications (Table 2).

Discussion

French investigators have improved the technical aspects of laparoscopic radical prostatectomy and claim that the procedure is a standardized therapeutic option

for clinically localized prostate cancer.[3,4,6–8] The potential advantages of this procedure include improved visualization of the anatomy, reduced blood loss, better preserved anatomical structures, and a shorter convalescence period.

The median blood loss in the present study was 540 mL, which is apparently less than that reported in open radical retropubic prostatectomy in Japan.[15] Only six percent of patients required allogeneic transfusion. The French group reported that mean blood loss was 514 mL in the initial 50 cases, which decreased to less than 300 mL with accumulated experience.[9] Optical magnification associated with more precise knowledge of the anatomy, and pneumoperitoneum probably explains the decreasing blood loss. This decreased blood loss, compared with that in other open prostatectomy series, might explain the low cardiovascular complication rate in our series with no deaths or myocardial infarctions and no cerebrovascular accidents. On the other hand, the major drawback of this procedure is the long operative time. The mean operative time was 427 min in the present series. Weber *et al.* reported a duration of 495 min in their initial nine cases, and they prematurely terminated the series because of their unacceptable results.[16] The French group reported a mean operative time of 268 min in their initial 50 cases, which was successfully reduced to less than 180 min by their accumulation of experience in over 500 cases.[9]

The incidence of patients who presented with at least one complication in this multi-institutional study was 37.3%, a figure disturbingly higher than that reported by Guillonneau *et al.*[9] An 8.1% incidence of bowel injuries was noted, including rectal injury in 10 cases (6.8%) and ileocolonic injury in two (1.4%). Three rectal injuries not detected intraoperatively caused serious complications such as peritonitis and ileus. Nine of the 12 bowel injuries (75%) required open conversion or postoperative open surgical repair. It has been reported that rectal injury occurs during section of the rectoapical Denonvilliers' fascia when posterior dissection has not been performed sufficiently close to the apex.[6,9] When such an injury is diagnosed intraoperatively, it can be easily repaired laparoscopically without the need for colostomy. Ureteral injury occurred in one case (0.7%). In this case, the ureter was sectioned after being mistaken for the vas deferens. It is important to identify the vas deferens based on its relationship with the seminal vesicle.[3–5] Bladder injury usually occurred when the prevesical space was entered, but it was easily repaired intraoperatively.

Early removal of the bladder catheter is expected in laparoscopic radical prostatectomy, because sufficient watertight vesicourethral anastomosis is possible under the field of optical magnification. Catheter removal is based on a surgeon-subjective analysis of the anastomosis. Guillonneau *et al.* showed that the catheter could be removed on day 3 if the anastomosis is immediately watertight.[9] In the present study, about half of the patients were catheter-free at postoperative day 7 or earlier. However, 25 patients (16.9%) required prolonged catheterization of 14 days or longer, suggesting that laparoscopic vesicourethral anastomotic procedure is still technically difficult. Convalescence seems to be shorter in laparoscopic radical prostatectomy than in open prostatectomy. About 70% of patients were able to walk and began oral intake at postoperative day 1.

With regard to the causes of perioperative death after major urologic pelvic surgery, risk from thromboembolic disease has been reported to be the most serious complication.[15] Initially, we were concerned that combining pelvic with laparoscopic surgery may increase the risk of thromboembolic disease. There were no thromboembolic complications such as pulmonary embolism or deep venous thrombosis. Reduced blood loss and shorter convalescence probably explain the extremely low rate of such serious complications.

In summary, we have reported in the present paper the early experience of laparoscopic radical prostatectomy performed at seven different institutions in Japan. Although the procedure is technically demanding, reduced blood loss and a shorter convalescence period can be expected. Surgeons should be aware of the disturbingly high morbidity rate related to early experience. The accumulation of experience and sharing of knowledge can possibly reduce the impact of learning curve required to perform this procedure competently.

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Original Article

Health-related quality of life after radical prostatectomy in Japanese men with localized prostate cancer

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Abstract

Purpose: We evaluated retrospectively health-related quality of life (HRQOL) after radical prostatectomy (RP) in Japanese men with localized prostate cancer.

Methods: The study was based on self-reported HRQOL of 280 patients. Patients were divided into seven groups: time 0 (T0), baseline before operation; T1, 1–3 months after RP; T2, 4–6 months after RP; T3, 7–12 months after RP; T4, 13–24 months after RP; T5, 25–36 months after RP; and T6, more than 36 months after RP. We measured the general and disease-specific HRQOL using the RAND 36-item Health Survey 1.0 (SF-36) and the University of California, Los Angeles Prostate Cancer Index (UCLA PCI).

Results: The general HRQOL of the postoperative groups was assessed by SF-36. The postoperative groups showed almost the same or higher scores than those of the baseline group. Urinary function scores decreased substantially after surgery. In contrast, there was no difference in urinary bother between the baseline and postoperative groups. Sexual function deteriorated substantially in all postoperative groups. Similarly, the sexual bother score significantly deteriorated after RP. The sexual bother score of men aged 65-years or younger was significantly worse than that of their counterparts in the T1–2 groups.

Conclusion: Despite reports of problems with sexual activity and urinary continence, general HRQOL was mostly unaffected by RP. Although there was a substantial decrease in urinary function, recovery from urinary bother was rapid. Since the deterioration of sexual function was marked through the postoperative period, careful attention should be paid to this issue during preoperative counseling, especially for younger patients.

Key words Health-related quality of life, Japanese men, prostate cancer, radical prostatectomy, self-reported questionnaire.

Introduction

Assessment of health-related quality of life (HRQOL) has an important role in outcome-based research and may strongly justify health care expenditure and influence treatment selection by patients. In the past 10 years, there has been a rapid increase of interest in HRQOL among patients with adenocarcinoma of the

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prostate. The incidence of early stage prostate cancer in Japanese men is clearly increasing although it is still lower than that in men in Western countries.[1] The rising incidence in Japan has been revealed by the widespread use of serum prostate-specific antigen (PSA) test. Some management options are available for patients with localized prostate cancer, including radical surgery, external-beam irradiation, brachytherapy, and expectant management of selected patients. Radical prostatectomy (RP) has particularly gained popularity among Japanese urologists over the last decade.[2] The success rate of RP is generally measured by the number of years that patients survive after the operation. For the patients themselves, however, the survival rate is not the only factor that affects their choice of medical treatment. A treatment that has a lower survival rate might be preferred to one with a higher survival rate if it can confer a higher quality of life. Accordingly, HRQOL studies can provide important information for patients and clinicians. To counsel patients effectively, physicians require accurate quality of life data. Armed with this information, patients are likely to feel more confident about their treatment choices.

To our knowledge, there have been few well-constructed studies that measure the HRQOL of Japanese men after undergoing RP by internationally validated methods such as the RAND 36-item Health Survey 1.0 (SF-36) and the University of California, Los Angeles Prostate Cancer Index (UCLA PCI). Therefore, the paper presented here addresses the issue of HRQOL in patients after RP in Japan. Our study will be able to determine the general tendencies of HRQOL in Japanese male patients after undergoing RP for localized prostate cancer. Moreover, the possibility of cultural or ethnic differences in HRQOL will be clarified.

Methods

Two hundred and forty-two patients with localized prostate cancer (T1–T3N0M0) underwent RP between January 1997 and April 2002 at Tohoku University Hospital and its five affiliated hospitals, and Kurashiki Central Hospital. Tumors were staged clinically according to the 1992 TNM classification.[3] All of the patient were informed of their cancer diagnosis before being asked to answer the questionnaire. Each patient who agreed to participate in the study received from their urologists a questionnaire, an informed consent form and a prepaid envelope for returning the questionnaire by mail.

Because no pretreatment HRQOL assessments were available, we chose patients who answered the assessment within 1 month before undergoing RP ($n = 55$). We analyzed a total of 297 Japanese men (Tohoku University Graduate School of Medicine, 50 patients; Miyagi Cancer Center, 69 patients; Tohoku Rosai Hospital, 25 patients; Sendai Shakaihoken Hospital, 25 patients; Hachinohe City Hospital, 30 patients; Ishinomaki Red Cross Hospital, 21 patients; and Kurashiki Central Hospital, 77 patients) with localized prostate cancer.

Patients were divided into seven time groups: time 0 (T0, $n = 55$), baseline before surgery; T1 ($n = 48$): 1–3 months after operation; T2 ($n = 37$), 4–6 months after operation; T3 ($n = 39$), 7–12 months after operation; T4 ($n = 40$), 13–24 months after operation; T5 ($n = 33$), 25–36 months after operation; and T6 ($n = 45$), more than 36 months after operation.

QOL methodology

We measured general and prostate-specific HRQOL as follows. General HRQOL was assessed with the SF-36,[4,5] which consists of 36 self-administered questions that quantify general HRQOL using eight multi-item scales. These scales comprise four physical domains (physical function, role limitations due to physical health problems, bodily pain and general health perception) and four mental domains (mental health, role limitations due to emotional problems, social function and vitality). The eight scales are scored separately from 0 to 100; a higher score representing better QOL. The SF-36 has been extensively tested and shown to be reliable. It has been translated from its original English into Japanese and its validity and reliability have been tested by Fukuhara *et al.* in Japanese people chosen randomly from different generations.[6]

Prostate-specific HRQOL was assessed using the UCLA-PCI.[7] It is a self-administered questionnaire with 20 questions that quantify prostate cancer-specific HRQOL in terms of six separate domains of urinary function and bother, bowel function and bother, and sexual function and bother. The urinary, bowel and sexual function scales focus on incontinence, proctitis and sexual difficulties, respectively, while the bother scales focus on how the patient is troubled by each dysfunction. The six scales are scored from 0 to 100; a higher score representing a better outcome. The UCLA-PCI has been translated into Japanese and its validity and reliability have been tested by Kakehi *et al.*[8]

Statistics

Quality of life scores for the various domains are shown as the mean ± SD in 0–100 scales, with a higher score representing better HRQOL. The analysis focused on comparing each HRQOL score of the postoperative

groups (T1–T6) with that of the preoperative group (T0). Differences in distribution of background variables were evaluated by non-parametric procedures (χ^2 and/or Mann–Whitney tests). The inspection value was shown using the average ± SD and the statistical analysis showed the *P*-value using the χ^2 square authorization and the Mann–Whitney *U*-test.

Results

The questionnaires were returned to us by 228 (94%) men who had undergone to RP and 52 (96%) who were awaiting RP.

Looking at the distribution of patients with prostate cancer according to selected demographic and clinical characteristics, the median postoperative follow-up time was 12 months (range 1–89) (Table 1). The average age of patients at the time of QOL survey was 68.9 ± 6.1 (range 51–83; median 69) and 73% ($n = 205$) of the patients were older than 65 years. When comparing these data in each group, it was found that patients in the T5 and T6 groups were significantly older ($P = 0.0004$) than those in the T0 group ($P = 0.0001$).

The study was retrospective and none of the groups was well-balanced in the rate of neoadjuvant therapy ablation, nerve-sparing and adjuvant therapy ablation.

Table 1 Background characteristics of 281 Japanese patients who underwent radical prostatectomy for localized prostate cancer

Time group	T0	T1	T2	T3	T4	T5	T6
No. patients	52	48	37	34	38	29	43
Working status							
Full-time worker	26	20	16	15	16	10	13
Part-time worker	7	3	4	4	6	3	5
Retired/no job	16	21	16	13	10	15	23
Unknown	3	4	1	2	5	1	2
P-value vs. T0	–	0.24	0.53	0.76	0.86	0.19	0.07
Marital status							
Married	46	44	33	29	33	25	38
Unmarried	1	2	0	0	1	0	0
Unknown	5	0	4	5	3	4	5
P-value vs. T0	–	0.49	0.41	0.44	0.77	0.48	0.38
Clinical stage							
T1	37	28	21	13	15	9	15
T2	13	18	12	20	15	15	22
T3	2	2	4	0	7	5	4
Unknown	0	0	0	1	1	0	2
P-value vs. T0	–	0.38	0.5	0.012	0.02	0.006	0.01
Age at survey							
Mean	66.5	67.5	66	66.5	67.7	70.8	70.6
SD	5.2	5.2	6.2	4.9	5.9	4.7	5.8
Max.	75	77	77	76	80	77	80
Min.	56	55	51	54	53	60	57
P-value vs. T0	–	0.37	0.65	0.96	0.33	0.0004	0.0001
Neoadjuvant therapy ablation							
No. patients (%)	13 (25)	19 (40)	17 (46)	20 (59)	25 (66)	23 (79)	35 (81)
P-value vs. T0	–	0.118	0.039	0.001	0.0001	<0.0001	<0.0001
Pathological stage							
Well	10	5	5	2	5	5	11
Moderate	36	38	30	27	22	19	28
Poor	6	5	2	4	11	5	3
Unknown	0	0	0	1	0	0	1
P-value vs. T0	–	0.61	0.68	0.37	0.21	0.94	0.83
Nerve sparing							
Bilateral	–	8	4	3	0	0	2
Unilateral	–	27	19	6	11	0	0
None	–	13	14	25	27	29	41
Adjuvant therapy ablation							
No. patients (%)	0 (0)	1 (2)	3 (8)	9 (26)	3 (8)	8 (28)	16 (37)

General HRQOL

Table 2 shows the general HRQOL scores. Of the eight SF-36 domains, physical function was lower in the T5 and T6 groups ($P = 0.005$) than in the T0 group ($P = 0.01$), but there was no significant difference between the T0 and T1–4 groups. Role limitation due to physical health problems in T1 scored worse than in the T0 group ($P = 0.03$), but there was no significant difference between the remaining groups and T0. Mental health in the T1 group had a relatively good score ($P = 0.07$), and furthermore, the T2 and T3 groups had a significant higher score than the T0 group ($P = 0.01$ and 0.03). Social function in the T2–4 groups had a slightly higher score than the T0 group ($P = 0.07$; $P = 0.06$; and $P = 0.07$, respectively). Other domains, including bodily pain, general health perception, role limitation due to emotional problems and vitality, showed no significant differences between the T0 group and any of the postoperative groups.

Urinary function and bother

Urinary function scored substantially lower in the T1 group and remained low in the T2–6 groups. Accordingly, urinary bother was slightly worse in the T1 group than in the T0 group ($P = 0.16$), but the remaining T2–6 postoperative groups had a similar urinary bother score to the baseline group (Table 3).

Figure 1 shows the differences in HRQOL scores for urinary function and bother between the younger (≤65 years) and older men (+65 years) of each group. Urinary function scores in the T0 and T1–3 groups were almost the same (Fig. 1a). In the T4 group, however, the scores of younger men were better than those of older men. (91.7 vs. 77.9, $P < 0.05$). In the urinary bother domain, there were

Table 2 RAND 36-item Health Survey 1.0 (Sf-36) scores of Japanese patients who underwent radical prostatectomy for localized prostate cancer†

Time group	Physical function	*P*-Value vs. T0	Mental health	*P*-Value vs. T0
T0	90.4 ± 8.9	–	68.8 ± 22.4	–
T1	86.0 ± 13.8	0.14	76.5 ± 19.4	0.07
T2	86.2 ± 13.4	0.27	80.4 ± 15.6	0.01
T3	83.8 ± 19.8	0.19	78.0 ± 17.5	0.03
T4	88.0 ± 16.1	0.71	76.0 ± 18.3	0.12
T5	81.7 ± 15.0	0.005	71.3 ± 22.7	0.63
T6	81.9 ± 18.8	0.01	76.3 ± 18.3	0.11
Time group	Role lim. physical		Role lim. emotional	
T0	86.4 ± 21.6	–	84.2 ± 21.2	–
T1	75.9 ± 25.0	0.03	76.8 ± 24.1	0.13
T2	83.4 ± 22.8	0.82	86.9 ± 19.8	0.57
T3	85.5 ± 24.3	0.83	86.3 ± 23.5	0.44
T4	86.4 ± 22.2	0.62	88.4 ± 20.7	0.32
T5	78.6 ± 27.2	0.44	79.3 ± 27.7	0.69
T6	83.4 ± 23.7	0.77	79.0 ± 26.0	0.41
Time group	Bodily pain		Social function	
T0	81.3 ± 18.5	–	81.4 ± 20.9	–
T1	74.3 ± 21.6	0.11	79.7 ± 23.7	0.79
T2	81.4 ± 17.2	0.97	90.8 ± 13.2	0.07
T3	82.0 ± 21.8	0.64	89.7 ± 15.8	0.06
T4	82.5 ± 17.0	0.86	88.8 ± 19.0	0.07
T5	86.6 ± 20.9	0.1	81.0 ± 24.5	0.85
T6	82.4 ± 18.9	0.67	84.0 ± 22.5	0.4
Time group	General health perception	Vitality		
T0	61.5 ± 12.8	–	69.3 ± 18.7	–
T1	65.0 ± 15.4	0.22	68.5 ± 19.7	0.91
T2	61.5 ± 14.2	0.91	75.5 ± 15.5	0.09
T3	62.5 ± 14.8	0.71	72.0 ± 20.7	0.31
T4	60.1 ± 13.5	0.63	69.6 ± 21.5	0.95
T5	57.4 ± 16.9	0.17	68.1 ± 23.8	0.83
T6	59.0 ± 14.9	0.35	67.6 ± 21.2	0.84

†Each domain is scored from 0 to 100 with higher scores representing better quality of life; lim, limitation.

Table 3 University of California Los Angeles Prostate Cancer Index (UCLA-PCI) scores of Japanese patients treated with radical prostatectomy†

Time group	Urinary function	*P*-Value vs. T0	Urinary bother	*P*-Value vs. T0
T0	94.5 ± 13.0	–	84.4 ± 23.6	–
T1	65.2 ± 27.5	<0.001	75.5 ± 29.8	0.16
T2	75.4 ± 26.8	<0.001	83.1 ± 25.0	0.86
T3	83.4 ± 23.6	0.007	88.2 ± 24.0	0.3
T4	81.5 ± 20.6	<0.001	85.5 ± 24.4	0.72
T5	74.6 ± 28.6	<0.001	82.8 ± 26.8	0.95
T6	70.3 ± 27.9	<0.001	80.2 ± 28.6	0.65
Time group	Bowel function		Bowel bother	
T0	89.8 ± 10.8	–	94.3 ± 12.6	–
T1	85.6 ± 16.0	0.33	94.8 ± 12.6	0.85
T2	84.1 ± 13.7	0.06	89.9 ± 17.1	0.34
T3	91.8 ± 13.5	0.14	89.0 ± 19.6	0.35
T4	88.7 ± 13.4	0.92	90.1 ± 18.9	0.48
T5	86.6 ± 13.7	0.54	93.8 ± 13.0	0.93
T6	83.4 ± 18.4	0.12	88.4 ± 19.9	0.27
Time group	Sexual function		Sexual bother	
T0	31.9 ± 22.9	–	76.4 ± 23.7	–
T1	5.5 ± 7.1	<0.001	54.7 ± 33.7	0.001
T2	6.3 ± 9.4	<0.001	52.7 ± 32.7	<0.001
T3	8.3 ± 12.0	<0.001	55.9 ± 39.0	0.03
T4	11.9 ± 15.4	<0.001	46.1 ± 36.1	<0.001
T5	5.8 ± 8.2	<0.001	60.3 ± 34.4	0.05
T6	6.1 ± 9.2	<0.001	70.3 ± 34.2	0.71

†Each domain is scored from 0 to 100 with higher scores representing better quality of life.

no significant differences in any postoperative group.

Bowel function and bother

No significant difference was observed in bowel function and bowel bother between T0 and any of the postoperative groups (Table 3).

Sexual function and bother

The sexual function score was substantially lower in T1 and remained at a deteriorated level in the T2–6 groups. Sexual bother similarly scored significantly lower in the T1–5 groups, but there were no differences between the T0 and T6 groups (Table 3).

Figure 2 shows an age group comparison between the sexual function and bother values of the younger and older men. Older men had more impaired sexual function at the baseline (23.3 vs. 46.1, $P < 0.05$) and both younger and older men continued to have lower scores in the T1–3 groups. In the T4 group, however, younger men had better scores (7.5 vs. 24.6, $P < 0.05$), suggesting better recovery of sexual function in this patient population. In contrast, the sexual bother scores of older men were better than those of younger men in the T1 and T2 groups (37.5 vs. 60.4, 33.3 vs. 65.9, respectively, $P < 0.05$).

Discussion

Although our study was based on a cross-sectional survey, it yielded several important findings. Despite various decreases in sexual and urinary function, the SF-36 scores of the T1 and T2 groups showed that general QOL was unaffected by RP except in the physical function domain. Patients in the T3–6 groups had a similar HRQOL to the patients in the T0 group, except for the physical function domain. This suggests that most patients rapidly recovered to their preoperative HRQOL within 6 months after surgery. The domain of role limitation due to physical problems, classified as the physical domain, scored slightly lower right after RP, but improved with time.

In our survey, physical function scores for the T5 and T6 groups were lower than that of the T0 group. However, the age of patients in the T5 and T6 groups were higher than those in the T0 group. This suggests the possibility that age had an influence on HRQOL. Social function and mental health, classified as the mental domain by SF-36, revealed that some postoperative

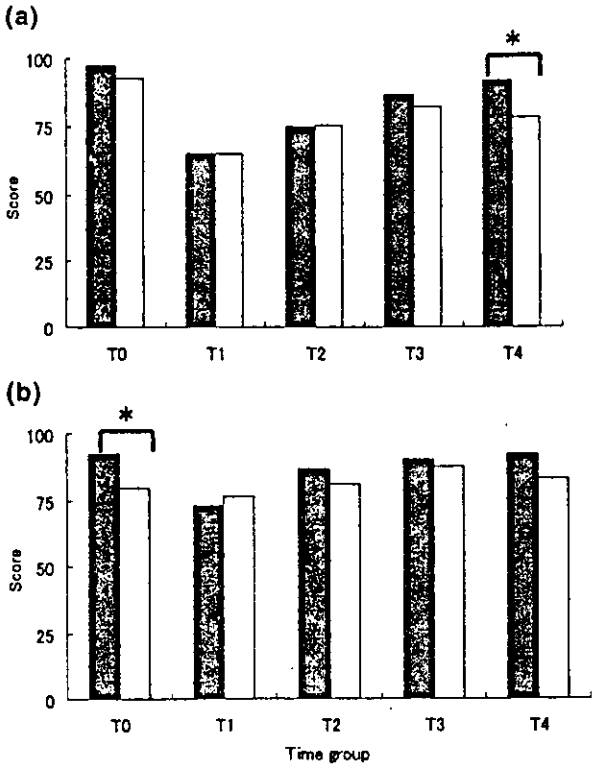

Fig. 1 Comparison of the mean University of California, Los Angeles Prostate Cancer Index (UCLA-PCI) scores for (a) urinary function and (b) urinary bother between younger men (■) and older men (□). *Statistically significant differences ($P < 0.05$).

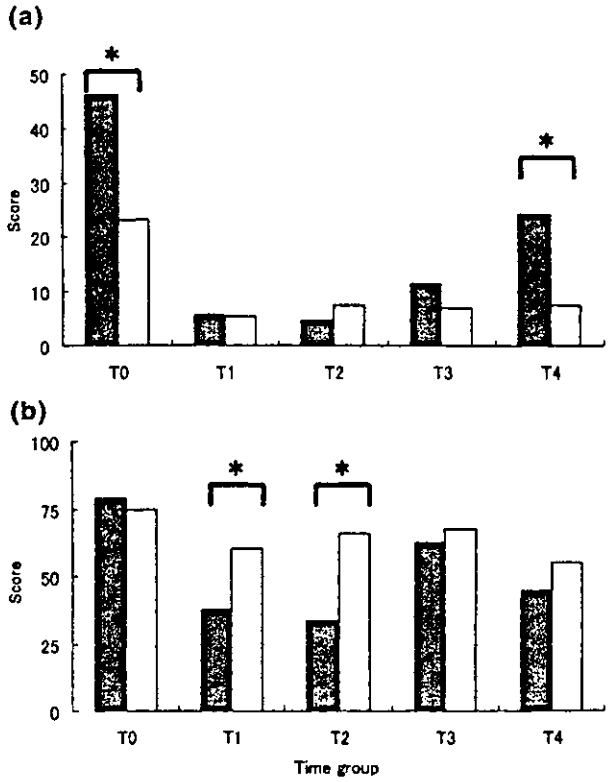

Fig. 2 Comparison of the mean University of California, Los Angeles Prostate Cancer Index (UCLA-PCI) scores for (a) sexual function and (b) sexual bother between younger men (■) and older men (□). *Statistically significant differences ($P < 0.05$).

groups had higher scores than the preoperative group. According to Talcott *et al.* SF-36 scores initially decreased during the postoperative stage, but recovered to baseline levels within 12 months.[9] Braslis *et al.* stated that tension levels prior to RP are likely to be elevated due to anticipation of major surgery, recent diagnosis of malignancy and fear of surgical outcome.[10] They found that following surgery, with the relief that accompanied the perceived cure, the tension level reduced and that a reduction in tension correlated with a reduction in feelings of confusion, depression and anger; a finding that is similar to ours.

Urinary incontinence, one of the most disabling complications of RP, has become an increasingly rare complication as a result of technical advances in the anatomical approach to RP. However, it should be noted that the reported incidence of incontinence after RP varies, both by the definition of incontinence and, most importantly, by data collection techniques. Catalona and Bigg defined continence as the absence of the need to wear pads to keep outer garments dry and included in this definition men with occasional leakage of one or two drops of urine with severe abdominal straining.[11] In their series, incontinence was observed in 6% of patients. Jonler *et al.* used a 24-h pad test, and revealing that 63% of patients had some incontinence 6 months after surgery.[12]

The present survey was performed using a self-reported questionnaire to exclude observer bias. According to our survey, a certain degree of recovery from postoperative incontinence can be anticipated, but it seems hard for male patients treated with RP to return to the baseline level completely. Early postoperative patients of T1 had the worst urinary function, which was expected, but T5–6 patients did not show sufficient recovery. This may be partly due to the operative procedure applied to these patients. Nerve-sparing techniques were not used in this patient population, and these groups were older than those of the baseline, which influenced the result. Interestingly, recovery from urinary bother was observed early in the T2 group and in

the remaining postoperative groups, showing that postoperative incontinence was, if present at all, minimal in the majority of the patients.

As expected, in terms of bowel function and bother, there was no significant difference between the preoperative and any of the postoperative groups.

Although the majority of postoperative patients reported a good general HRQOL, a significant deterioration of sexual function was observed in all the postoperative groups, and this deterioration remained low in the T5–6 groups. This may be explained by the fact that these groups did not undergo nerve-sparing procedures and were composed of relatively elderly patients. Furthermore, about two-thirds of patients in the T5–6 groups received androgen ablation. Kakehi *et al.* stated that Japanese patients with decreased sexual activity felt less sexual bother than American patients, and moreover, poor sexual function had a lower association with the SF-36 scores in Japanese compared with American patients.[8] In our survey, however, all postoperative groups except for T6 had lower sexual function and bother scores compared to the baseline group. The reason why patients in the T6 group had high urinary and sexual bother scores, even though they had reduced function, might be explained by their development of understanding of how to manage their disease over time.

We found that men older than 65-years in particular might achieve baseline levels of sexual bother more rapidly than younger men. We emphasize that patients over 65 years who underwent RP felt less sexual bother despite their lower sexual function, but younger patients felt differently, possibly because they had higher expectations about sexual function and, therefore, required more time.

Sub-analysis indicated that PSA recurrence and androgen ablation may affect HRQOL. Wei *et al.* observed lower SF-36 and UCLA PCI scores in men with PSA recurrence.[13] In our study there was no significant difference, except for sexual function (data not shown), in patients who had undergone adjuvant androgen deprivation therapy and those who had not.

Litwin *et al.* investigated the longitudinal recovery of QOL after RP in 247 men with localized prostate cancer.[14] They found that most QOL recovery occurs soon after RP except in several domains, including urinary and sexual function, which continue to improve even as long as 2 years after RP. We previously reported the impact of RP on Japanese QOL 12 months or longer after surgery.[15] According to our study, general HRQOL does not appear to be compromised following RP, but most patients were dissatisfied with their postoperative sexual function. We should emphasize that in preoperative counseling, greater emphasis needs to be placed on the risk of postoperative erectile dysfunction.

Our study had several limitations. First, because it was a retrospective study, there was a lack of information about pretreatment functioning among postoperative participants. Second, preoperative patients do not always represent an ideal control group. This is because patients awaiting major surgery may have already experienced a reduction in QOL because they may have already been informed of their cancer diagnosis and decided to undergo treatment.[15] Third, we did not distinguish whether or not nerve-sparing procedures were performed and did not distinguish between neoadjuvant or adjuvant hormonal therapy. These factors may be significant predictors of HRQOL recovery. Gralnek *et al.* reported much higher levels of potency and continence after nerve-sparing RP.[16] Finally, patients who chose not to participate may have had HRQOL outcomes that were either better or worse than those in the study presented here.

Despite these limitations, our study using SF-36 and UCLA PCI questionnaires, which are both used worldwide, could provide useful information about patient-centered outcome evaluations. Ethnic or cultural differences related to localized prostate cancer treatment also appear to be important. The UCLA PCI has been translated into Spanish, Dutch, and French.[6] Cross-cultural comparative studies of the changes in disease-specific HRQOL using common instruments will certainly contribute to the global advancement of outcome assessment following the treatment for localized prostate cancer.[7] We are currently collecting prospective multi-institutional outcome data on RP, comparing nerve sparing and non-nerve sparing, laparoscopic prostatectomy, and radiotherapy. HRQOL research continues to evolve, providing better information to patients and physicians.

Conclusion

We investigated HRQOL after RP in Japanese men with the use of a cross-sectional survey. Despite reports of problems with sexual function and urinary continence, general HRQOL was mostly unaffected by RP. Although there was a substantial decrease in urinary function, recovery from urinary bother was rapid. The deterioration of sexual function was marked throughout the postoperative course. Careful attention should be given to this issue in preoperative counseling of patients, especially in younger patients. A prospective longitudinal study with a larger patient population is warranted to

further elucidate the patient-centered outcome in Japanese men undergoing RP.

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Possible Mechanism of DexamethasoneTherapy for Prostate Cancer: Suppression of Circulating Level of Interleukin-6

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BACKGROUND. Glucocorticoids may have favorable effects on prostate cancer patients showing clinical and/or biochemical failure after androgen ablation. The efficacy and mechanisms of dexamethasone therapy as possible alternative endocrine therapy were investigated.

METHODS. Twenty five patients with prostate cancer treated by androgen ablation and showing a steady increase in serum prostate specific antigen (PSA) were treated with low-dose dexamethasone.

RESULTS. Of 25 patients, 11 demonstrated 50% or more decline of serum PSA and 9 showed improvement of pain on dexamethasone therapy. Of 8 patients who responded to dexamethasone thearpy, 5 had 80% or more decrease in serum interleukin-6 (IL-6). In contrast, none of 8 non-responders showed remarkable IL-6 suppression. Response of PSA was not correlated to the changes in serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, or androstendione.

CONCLUSIONS. Significant suppression of serum IL-6, probably through inhibition of androgen-independent activation of androgen receptor, may be one of the mechanisms for the effect of dexamethasone therapy in prostate cancer patients with progressive disease. *Prostate 56: 106–109, 2003.* © 2003 Wiley-Liss, Inc.

KEY WORDS: **prostate cancer; androgen ablation; glucocorticoid; interleukin-6; prostate specific antigen**

INTRODUCTION

For the management of advanced prostate cancer, endocrine therapy by androgen ablation is generally effective as an initial treatment. However, when progression occurs after initial endocrine therapy, optimal therapy has not been established. Recently, it was demonstrated that antiandrogen withdrawal and administration of another antiandrogen or glucocorticoid might have favorable effects on patients who had been treated with androgen ablation and had shown clinical and/or biochemical failure [1–6]. Thus, "hormone-refractory" prostate cancer is thought to include patients with a spectrum of diseases. Based on these findings, Scher et al. [3] advocated new classification of hormonal sensitivity of prostate cancer: (i) hormone-naïve; (ii) androgen-independent and hormone-sensitive; and (iii) androgen-independent and hormone-insensitive. In the present study, the efficacy of dexamethasone as an alternative endocrine therapy is examined by responses in serum prostate specific antigen (PSA) and pain relief. In addition, the mechanisms of dexamethasone therapy are investigated.

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MATERIALS AND METHODS

A total of 25 patients with prostate cancer who had been treated with androgen ablation (surgical castration or LHRH agonist) and had shown biochemical failure (a steady increase in serum PSA) were included in the present study. Upon biochemical failure, the patients were treated with dexamethasone (initially 1.5 mg/day, then tapered to 0.5 mg/day). In patients treated with surgical or medical castration plus antiandrogen, antiandrogen withdrawal syndrome was assessed for at least 4–8 weeks by the cessation of the antiandrogen before dexamethasone therapy; and treatment with LHRH agonist was not discontinued. Serum PSA levels were determined with the Tandem-R PSA Assay (Hybritech, Inc., San Diego, CA). The clinical effect of dexamethasone therapy was evaluated based on improvement of pain. Patients who showed 50% or more decline of serum PSA and/or improvement of pain estimated by decrease in dose or change of analgesics were defined as responders to dexamethasone therapy. The changes in serum testosterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstendione, ACTH, cortisol and interleukin-6 (IL-6) were measured in relation to the effect of dexamethasone therapy.

Statistical Analysis

Statistical analysis was performed by the Mann–Whitney U-test and chi-square test. $P < 0.05$ was considered significant.

RESULTS

At initial diagnosis, histological examination of the tumor showed 3 well differentiated, 10 moderately differentiated, and 10 poorly differentiated adenocarcinomas. Histological grade of the tumor was unknown in two patients. The methods of initial endocrine therapy consisted of surgical or medical castration alone in 7, castration plus chlormadinone acetate in 11, castration plus flutamide in 6, and castration plus bicalutamide in 1. As second or third line endocrine therapy, alternative antiandrogen was administered; chlormadinone acetate in 4, flutamide in 7, and bicalutamide in 12. The duration of endocrine therapy ranged from 5 to 81 months with a mean of 27.4 months. Patients' ages at the start of dexamethasone therapy ranged from 47 to 82 years with a mean of 69 years. The median serum PSA level at dexamethasone therapy was 262 ng/ml with a range of 8.4–4,100 ng/ml.

TABLE I. Change of Serum PSA and Clinical Symptoms by DexamethasoneTherapy in Prostate Cancer Patients Who Showed Biochemical Failure

	Pain relief by dexamethasone therapy		
≥50% PSA decline	Effective	Not effective	No symptom
Yes	8	0	3
No	1	12	1
Total	9	12	4

Of 25 patients, 11 (44%) demonstrated 50% or more decline of serum PSA by dexamethasone therapy. The average duration of responding period was 5.1 (range: 1–8) months. Eight patients showing 50% or more decline of PSA and one patient without remarkable decline of PSA revealed improvement of pain relief (Table I). The response of dexamethasone therapy was not related to serum PSA levels at the start of therapy, the duration of previous endocrine therapy, or the previous occurrence of antiandrogen withdrawal syndrome (Table II).

Serum testosterone levels were suppressed to within the castrate range in all patients examined (data not shown). The response to dexamethasone therapy was

TABLE II. Comparison of Clinical Characteristics Between Responders and Non-Responders to DexamethasoneTherapy in Prostate Cancer Patients Who Showed Biochemical Failure

Factors	Responders[a]	Non-responders
Number of patients	12 (48%)	13 (52%)
PSA at dexamethasone therapy (ng/ml)	657.6 ± 645.6	774.1 ± 1172.3
Duration of endocrine therapy (months)	32.3 ± 26.6	23.0 ± 17.2
Previous antiandrogen withdrawal syndrome		
Yes	2	2
No	7	11
Not evaluable	3	0

[a]Responders: patients who showed 50% or more decline of serum PSA and/or improvement of pain.