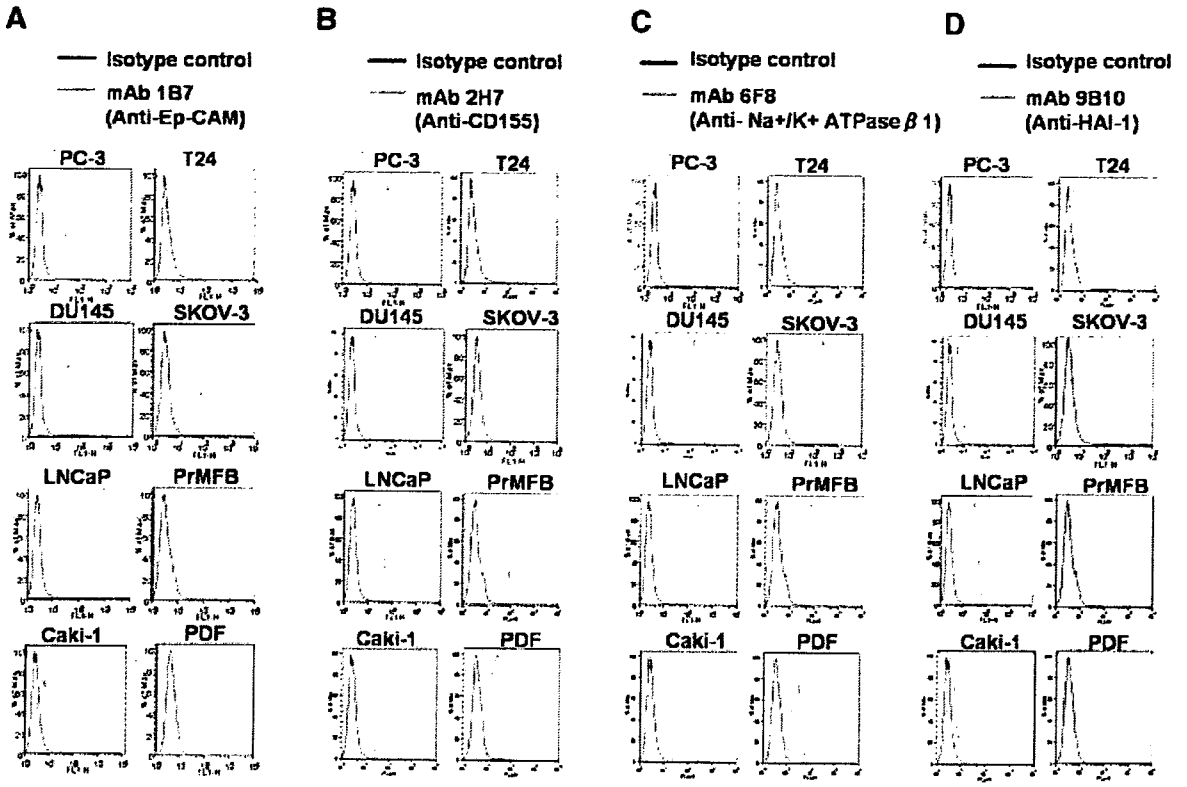

Fig. 7. Reactivities of established mAbs with various human cell lines. **A**: Antigen of mAb 1B7 was expressed on the surface of PC-3, DU145, LNCaP, Caki-1, T24, and SKOV-3 but not PrMFB and PDF. **B,C**: Antigens of mAbs 1B7 and 6F8 were expressed on the surface of each cell line. **D**: Antigen of mAb 9B10 was expressed on the surface of PC-3, DU145, LNCaP, Caki-1, and T24 but not SKOV-3, PrMFB, or PDF.

DISCUSSION

Volspers et al. [6] constructed a Z33-modified adenovirus vector and reported that the transduction efficiency of this modified vector in epidermal growth factor receptor (EGFR)-expressing cells was strongly and dose-dependently enhanced by combination with an EGFR-specific monoclonal antibody. They suggested that antibody-mediated targeting of the Z33-modified adenovirus vector could be applied for directed gene transfer to a wide variety of cell types by simply changing the target-specific antibody. Tanaka et al. [8] evaluated, both in vitro and in vivo, the extent of retargeting toward and therapeutic effectiveness against carcinoembryonic antigen (CEA)-positive gastric cancers when using the fully human CEA antibody complex with Adv-FZ33. They generated Ax3CAUP-FZ33 (UP-FZ33), an Adv-FZ33 derivative vector expressing a therapeutic gene (*Escherichia coli* uracil phosphoribosyltransferase) that converted 5-fluorouracil (5-FU) directly to 5-fluoro-UMP. UP-FZ33 with the anti-CEA mAb enhanced the cytotoxicity of 5-FU by 10.5-fold in terms of the IC_{50} against a CEA-positive gastric cancer cell line compared with control IgG4. In a nude mouse peritoneal dissemination model, tumor growth in mice treated by UP-FZ33 premixed with the anti-CEA mAb was significantly suppressed, and the median survival time was significantly longer than in the control group.

Surface antigens may be a viable target for antibody-mediated gene therapy. Although, PSA is a clinically important biomarker in prostate cancer [10,11], PSA is not a surface antigen [12]. Although, prostate-specific membrane antigen (PSMA) [13] is a type II membrane antigen, the PSMA expression pattern is not fully restricted to the prostate [14,15]. Therefore, we investigated target molecules amenable to gene therapy with Adv-FZ33. In this study, we immunized mice with three human cell lines that were androgen-independent (PC-3 and DU145) or androgen-dependent (LNCaP) [16], for generating various types of mouse mAbs. We have performed to screening the target antibodies using human prostate cancer cell line PC-3. Although, our Adv-FZ33 has intact CAR-binding structure and retains CAR-binding ability, CAR protein is downregulated in the highly tumorigenic PC-3 cell line [17] and the transduction efficiency of adenovirus is quit low (Fig. 6). Furthermore, PC-3 does

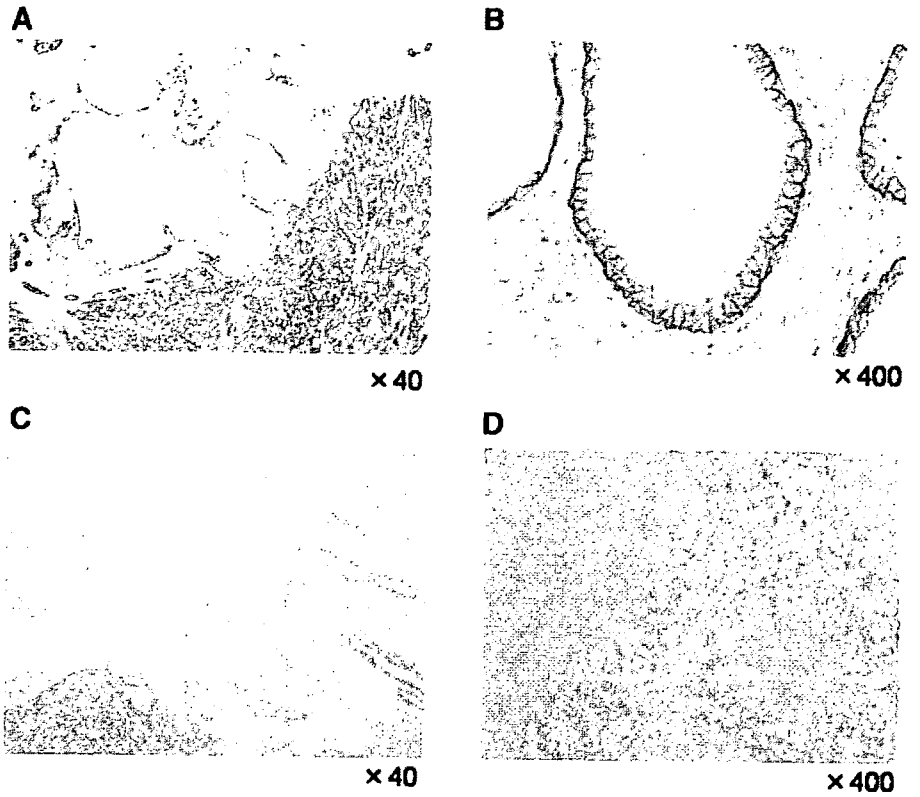

Fig. 8. Immunohistochemical findings for prostate cancer cells and normal epithelial cells of the prostate. **A**: Prostate cancer and normal epithelial cells shows strong immunoreactivity for mAb IB7. **B**: Basolateral cell surface of normal epithelium shows strong immunoreactivity for mAb IB7. **C**: Prostate cancer shows strong immunoreactivity for mAb IB7 but normal epithelial cells do not. **D**: Normal epithelial cells are not stained. Stromal cells are not stained in each sample.

not express PSMA. The first aim of this study is to target adenovirus to resistant cell line PC-3.

We purified four different mAbs and confirmed high transduction efficiency by flow cytometry and chemiluminescent β-Gal reporter gene assay. The target molecules of mAbs 1B7, 2H7, 6F8, and 9B10 were Ep-CAM, CD155, Na,K-ATPase β1, and HAI-1, respectively. CD155 and Na,K-ATPase β1 found to be widely expressed by flow cytometric analysis are inappropriate molecules for tumor targeting. The anti-Ep-CAM antibody mAb 1B7 and anti-HAI-1 antibody mAb 2H7 showed reactivity with cancer cell lines other than fibroblast cell lines. We could not find reactivity with prostate cancer samples for mAb 2H7, 6F8, or 9B10. These mAbs may be unsuitable for staining of samples fixed in formalin. In mAb 1B7, we found that Ep-CAM expression on prostate cancer cells was stronger than on normal epithelial cells, but not significantly. In 1979, Ep-CAM was discovered in a search for novel cell surface antigens expressed on neoplastic tissue [18]. Ep-CAM is known to be expressed on the basolateral cell surfaces of selected normal epithelia and many carcinomas [19–22]. Of particular interest, overexpression of Ep-CAM has been reported in prostate cancer [21,23]. Clinical trials of mAbs directed against Ep-CAM for immunologic therapy have been conducted in patients with colon cancer [24]. Recently, clinical phase I study with anti-Ep-CAM humanized IgG1 have been performed in patients with hormone refractory prostate cancer by Oberneder et al. [25]. Heideman et al. [26] showed that Ep-CAM targeted vectors using bispecific antibodies against the adenovirus fiber-knob protein, and Ep-CAM may be useful for gastric and esophageal cancer-specific gene therapy. HAI-1 is a novel Kunitz-type serine protease inhibitor first reported in 1997 [27]. Although, HAI-1 is broadly expressed in epithelial cells of most human tissues [28,29], Knudsen et al. [30] reported that its expression was significantly increased in localized prostate cancer and was present in most prostate cancer metastases compared to normal prostate glands. Furthermore, HAI-1 overexpression in prostate cancer was predictive of prostate-specific antigen recurrence. Nagakawa et al. [31] demonstrated that significantly increased serum levels of HAI-1 were detected in patients with prostate cancer, indicating that HAI-1

would be a potential tumor marker for prostate cancer. Ep-CAM and HAI-1 overexpressed in prostate cancer may be potential targets for prostate cancer gene therapy with Adv-FZ33, although therapeutic effectiveness must be evaluated as well. In future clinical application, we would like to use Adv-FZ33 premixed with prostate cancer targeting mAb prior to injection. This method seems to be more practical for administration systemically.

In addition to mAb 1B7 and 9B10, we may be able to establish new prostate cancer-specific mAbs through the hybridoma screening system that was designed in this study. Previously, Lampe et al. [32] performed fusions 25 times and developed three mAb directed against prostate associated antigens that might identify potential new therapeutic targets through screening of circa 25,000–50,000 hybridomas. We evaluated only 2,500 wells through three fusions and identified potential four target molecules. Overall, this approach of inductive method using FZ33 fiber-modified adenovirus is reliable strategy for screening useful mAbs that recognize target molecules in prostate cancer gene therapy as well as antibody therapy and diagnosis.

CONCLUSIONS

We established hybridoma from mice immunized with prostate cancer cell lines and selected anti-Ep-CAM mAb and anti-HAI-1 mAbs. Using Adv-FZ33, these mAbs increased transduction efficiency to prostate cancer cells. Gene transduction via Ep-CAM and HAI-1 may be a novel strategy for treatment of prostate cancer.

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Impact of Unilateral Sural Nerve Graft on Recovery of Potency and Continence Following Radical Prostatectomy: 3-Year Longitudinal Study

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Purpose: We conducted a 3-year longitudinal study assessing the impact of unilateral sural nerve graft on recovery of potency and continence following radical prostatectomy.

Materials and Methods: A total of 113 patients undergoing radical retropubic prostatectomy were classified into 3 groups according to the degree of nerve sparing, that is unilateral nerve preservation with contralateral sural nerve graft interposition, bilateral nerve sparing and unilateral nerve sparing. Urinary continence and potency were estimated by the UCLA Prostate Cancer Index questionnaire.

Results: Patients in the nerve sparing plus sural nerve graft group were younger than those in the bilateral nerve sparing or unilateral nerve sparing groups. At baseline the unilateral nerve sparing plus sural nerve graft group and the bilateral nerve sparing group reported better sexual function than the unilateral nerve sparing group (62.1 and 61.5 vs 49.9, $p < 0.05$). The bilateral nerve sparing group showed more rapid recovery than the unilateral nerve sparing plus sural nerve graft group after radical retropubic prostatectomy ($p < 0.01$). After 24 months there were no significant differences observed between the bilateral nerve sparing and the unilateral nerve sparing plus sural nerve graft group (28.7 vs 32.9). The bilateral nerve sparing group reported a better sexual function score than the unilateral nerve sparing group throughout the postoperative period ($p < 0.05$). The bilateral nerve sparing group maintained significantly better urinary function at 1 month after radical retropubic prostatectomy than the unilateral nerve sparing plus sural nerve graft group ($p < 0.05$). After 3 months these groups were almost continent. The unilateral nerve sparing group reported lower urinary function scores during the first year compared to the other groups.

Conclusions: The nerve graft procedure may contribute to the recovery of urinary function as well as sexual function after radical retropubic prostatectomy. This finding needs to be validated in a randomized trial.

Key Words: prostatic neoplasms, prostatectomy, sural nerve, urinary incontinence, impotence

Prostate cancer has a significant impact on HRQOL. Although a variety of treatment options are available including external beam radiation, brachytherapy and hormonal ablation, radical prostatectomy is considered a safe and effective treatment for localized prostate cancer.[1] Urinary incontinence and erectile dysfunction represent the principal sources of postoperative adverse events for patients who have undergone RP. Because initiation of penile erection is a neurovascular event, preservation of the cavernous nerves during RP is the most important factor for the recovery of erectile function following RP. Catalona et al reported excellent results with overall postoperative potency rates of 68% and postoperative continence rates of 92%.[2] With low volume and low stage disease nerve sparing does not compromise surgical margins. However, nerve sparing might not be appropriate in men with high grade tumors or palpable disease extending toward the neurovascular bundle. Interposition of sural nerve graft to replace resected cavernous nerves during RP confers a greater chance of recovering erectile function than without grafts. Scardino and Kim reported that with nerve grafting for the side of NVB resection, erectile function of the patients undergoing unilateral nerve sparing returns to a level approximating bilateral nerve sparing.[3] On the other hand, several studies have shown that preservation of the NVB is also associated with improved recovery of urinary control after RP.[4,5]

Although several investigators have reported short-term results with nerve grafting, there is still controversy regarding the long-term outcomes of nerve grafts following RP. We report longer term patterns of HRQOL (ie potency and continence) recovery during the first 3 years after RP using a validated questionnaire.

PATIENTS AND METHODS

Patient Population and Operative Technique

From January 2002 to December 2004 a total of 145 patients with newly diagnosed localized prostate cancer were treated with RP at Tohoku University Hospital. There were 15 patients with nonnerve sparing and 3 with bilateral sural

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nerve graft excluded from analysis. An additional 14 patients were excluded who received initial hormonal ablation, leaving 113 candidates for this study. These patients were classified into 3 groups according to the degree of nerve sparing, that is unilateral nerve preservation with contralateral sural nerve graft interposition group (UNS plus SNG), a bilateral nerve sparing group and a unilateral nerve sparing group. The indications for nerve sparing procedure depended on preoperative factors (clinical stage, transrectal ultrasound findings, number and Gleason score of positive biopsies, PSA or patient preference) and intraoperative factors, prioritizing cancer control. All patients who had minimal erectile dysfunction and in whom nerve resection was anticipated were offered SNG and counseling regarding the risks, benefit and likely impact on postoperative potency recovery. Patients ultimately decided whether SNG interposition would be performed. In our study preservation of the NVB was assigned based on the results of intraoperative electrostimulation as reported by Kurokawa et al.[6]

Quality of Life Assessment

Urinary continence and potency were estimated using the urinary and sexual function and bother domains of the UCLA PCI, which assesses prostate specific HRQOL.[7] The questionnaire had already been translated into Japanese, and the validity and reliability had been previously tested.[8] All patients were informed of their cancer diagnosis before being asked to fill out the questionnaires. Followup interviews were conducted in person at scheduled study visits of 1, 3, 6, 12, 18, 24 and 36 months after RP. All patients who agreed to participate in this study received a questionnaire, an informed consent form and a prepaid postage envelope for returning the questionnaire. They voluntarily provided the self-reported questionnaire by mail.

Statistical Analyses

At baseline a comparison among the 3 groups was performed using the chi-square test or 1-way analyses of variance (ANOVA). UCLA PCI scores for the various domains are shown as the mean plus or minus standard deviation (SD) on 0 to 100 scales, with higher scores always representing better outcomes. Statistical analyses were performed using repeated ANOVA or the Mann-Whitney U test for groups to compare the effects of each treatment, with $p < 0.05$ considered statistically significant.

RESULTS

Complete demographic and clinical data were available for participants at enrollment. Table 1 compares these data among 3 groups. The age of the UNS plus SNG group was statistically lower than that of the BNS or UNS groups ($p < 0.05$ for each). The 3 groups were comparable in terms of preoperative PSA, Gleason scores and pathological tumor stage. Each group showed similar levels of comorbidities and sociodemographic characteristics. Some patients (50.4%) experienced comorbidities, the most common of which were hypertension (26%), diabetes (7%), gastrointestinal (18%), cardiovascular (9%) disease and other kinds of carcinoma (5%), but these comorbidities have been well controlled. There were 6 patients (5%) who received salvage therapy because of biochemical recurrence. All patients received bicalutamide or radiotherapy. No patients used vacuum erection devices.

TABLE 1. *Demographic and clinical characteristics of study population*

	UNS + SNG	BNS	UNS	p Value
No. pts	19	34	60	
Age at survey:				
Mean ± SD	58.0 ± 5.4	64.1 ± 5.8	65.1 ± 5.7	<0.001*
Median	58	64	65	
Range	48–69	47–73	51–77	
PSA at diagnosis (ng/ml):				
Mean ± SD	8.0 ± 4.7	8.3 ± 8.9	8.8 ± 6.7	0.878†
Median	6.5	6.4	7.3	
Range	3.4–21.8	3.1–53.0	2.1–52.7	
No. clinical tumor stage:				0.046†
T1	14	30	39	
T2	3	4	19	
T3	2	0	2	
No. pathological tumor stage:				0.183†
T2	16	32	48	
T3	3	2	12	
No. Gleason score:				0.857†
6 or Less	8	14	28	
7 or Greater	11	20	32	
No. salvage therapy ablation (%)	1 (5)	2 (5)	3 (5)	0.577†
No. comorbidities:				0.607†
None	12	18	27	
1–2	6	13	29	
3+	1	3	4	
No. working status:				0.461†
Full-time	10	11	29	
Part-time	4	5	6	
Retired/no job	5	14	25	
No. marital or relationship status:				0.842†
Married or living with spouse or partner	17	31	56	
Unmarried or not in significant relationship	2	3	4	

* Mann-Whitney U test.
† Chi-square test.

TABLE 2. *UCLA PCI scores*

	Mean ± SD			
	UNS + SNG	BNS	UNS	p Value
Urinary function:				<0.001
Baseline	95.9 ± 11.9	95.5 ± 12.8	97.4 ± 6.8	
1 Mo	51.5 ± 32.1*	66.8 ± 23.9*	56.4 ± 26.1*	
3 Mos	73.4 ± 27.6*	71.4 ± 21.1*	61.2 ± 25.4*	
6 Mos	82.3 ± 24.8*	84.2 ± 16.9*	75.8 ± 30.1*	
12 Mos	84.0 ± 22.1*	84.2 ± 15.3*	76.2 ± 24.3*	
18 Mos	88.8 ± 14.3*	87.0 ± 14.6*	81.3 ± 19.9*	
24 Mos	89.0 ± 12.9	88.7 ± 14.2	86.4 ± 18.9*	
36 Mos	90.6 ± 6.5	88.5 ± 20.6	86.3 ± 13.6*	
Urinary bother:				<0.001
Baseline	93.3 ± 11.6	91.1 ± 13.6	94.5 ± 8.9	
1 Mo	58.3 ± 38.6*	74.0 ± 25.0*	65.5 ± 28.6*	
3 Mos	81.9 ± 24.7*	79.6 ± 25.4*	70.3 ± 34.4*	
6 Mos	83.8 ± 20.9*	83.3 ± 28.4*	77.4 ± 29.8*	
12 Mos	86.8 ± 22.0	86.4 ± 14.6	82.1 ± 24.0*	
18 Mos	91.7 ± 10.5	89.6 ± 12.3	85.3 ± 20.5	
24 Mos	93.3 ± 9.0	89.4 ± 9.3	83.0 ± 16.6	
36 Mos	91.7 ± 7.9	88.5 ± 12.2	87.5 ± 16.5	
Sexual function:				<0.001
Baseline	62.1 ± 11.6	61.5 ± 16.9	49.9 ± 19.4	
1 Mo	7.2 ± 7.6*	12.7 ± 20.8*	6.5 ± 8.2*	
3 Mos	7.9 ± 4.4*	16.0 ± 18.6*	6.7 ± 8.6*	
6 Mos	11.9 ± 6.8*	22.6 ± 17.2*	8.4 ± 10.1*	
12 Mos	16.7 ± 12.6*	24.4 ± 17.4*	13.2 ± 14.0*	
18 Mos	24.2 ± 12.0*	25.5 ± 21.5*	13.9 ± 12.0*	
24 Mos	27.7 ± 10.4*	26.5 ± 20.9*	12.7 ± 12.9*	
36 Mos	32.9 ± 17.0*	28.7 ± 28.7*	13.4 ± 13.4*	
Sexual bother:				<0.001
Baseline	80.3 ± 21.7	81.9 ± 20.3	78.8 ± 22.7	
1 Mo	31.3 ± 27.2*	45.6 ± 31.1*	48.4 ± 32.4*	
3 Mos	33.3 ± 35.4*	48.9 ± 33.5*	47.8 ± 36.4*	
6 Mos	44.5 ± 30.0*	52.1 ± 28.1*	50.2 ± 34.9*	
12 Mos	39.0 ± 23.4*	59.4 ± 30.5*	48.1 ± 32.2*	
18 Mos	51.7 ± 19.2*	54.4 ± 28.6*	55.0 ± 25.7*	
24 Mos	50.0 ± 19.6*	50.0 ± 20.4*	45.0 ± 29.2*	
36 Mos	58.3 ± 23.6*	45.8 ± 30.0*	54.6 ± 30.6*	

* Statistically significant changes from baseline ($p < 0.05$).

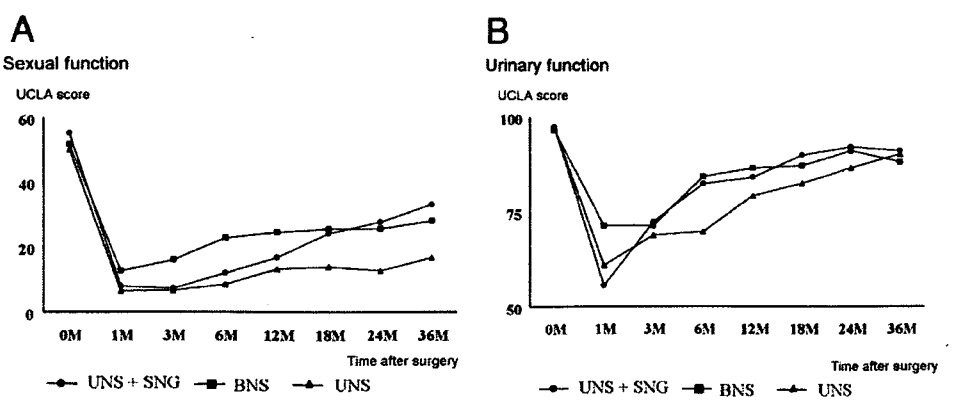
Table 2 presents the recovery of urinary and sexual domains of each group. At baseline the UNS plus SNG and the BNS groups reported better sexual function than the UNS group (62.1 and 61.5 vs 49.9, respectively, $p < 0.05$). The BNS group showed more rapid recovery than the UNS plus SNG group within 12 months ($p < 0.01$, repeated ANOVA). However, after 24 months there were no significant differences between the UNS plus SNG and BNS groups. The UNS plus SNG group continued to show improvement even in the third year. The BNS group had a better sexual function score than the UNS group throughout the postoperative period at 3 years. At 36 months 25% of the UNS plus SNG group and 28% of the BNS group considered the ability to function sexually as fair or good compared with 12% of patients with UNS alone. In addition, 60% of the UNS plus SNG group and 55% of the BNS group could achieve an erection more than half the time vs 18% of patients with UNS alone. All of the surgery groups had substantial impairment in the sexual bother domains throughout the postoperative period (Mann-Whitney U test $p < 0.01$ for each point). The UNS plus SNG group claimed lower sexual bother scores than the other 2 groups at 1 and 3 months postoperatively (both $p < 0.05$).

When considering urinary continence no significant differences were observed in urinary function and bother scores at baseline for each group. The BNS group maintained significantly better urinary function at 1 month after RP than the SNG group (66.8 vs 51.5, $p < 0.05$). After 12 months the BNS and SNG groups were almost continent. The UNS group reported lower urinary function scores during the first year than the other groups. Urinary bother at 1 and 3 months was significantly worse than baseline in all 3 groups. However, at 6 months it returned to the baseline in the UNS plus SNG and BNS groups. The UNS group reported lower urinary function scores during the first year than the other groups.

Because age affects sexual and urinary function, we also performed age matched analyses. Among patients younger than 66 years 18 were in the UNS plus SNG group, 21 in the BNS group and 26 in the UNS group. With age matched analysis there was no difference in sexual function at baseline among the 3 treatment groups. The same tendency that the BNS group had more rapid recovery of urinary and sexual function than the SNG group was observed just after RP. The UNS plus SNG group continued to show improvement, and the differences lost significance in sexual and urinary function by 12 and 3 months, respectively (see figure).

DISCUSSION

Nerve grafting is a surgical technique that has been used for decades. The grafted nerve serves primarily as a channel or scaffold for regenerating axons to reestablish the connection between the severed segments. To our knowledge this is the largest published series of sural nerve grafts performed at a



Sequential changes in average sexual function (*A*) and urinary function (*B*) scores in unilateral nerve sparing with contralateral sural nerve graft group bilateral nerve sparing group and unilateral nerve sparing group for age matched comparison.

single institution with the longest clinical followup. Our study has several important findings. With selective graft replacement of a unilateral nerve resection, sexual function appears to recover to a level approximating that of bilateral nerve sparing and superior to that of unilateral resection without grafts. Furthermore, the present longitudinal study revealed different profiles in terms of recovery of sexual function after RP. The exact recovery time for return of full sexual function after nerve sparing RP is still underestimated, and the majority of patients do not recover erectile function as early as urinary continence. Walsh reported that maximal erectile recovery was not witnessed until a mean period of 18 months after bilateral nerve sparing RP because a number of factors such as thermal damage, ischemic injury and the local inflammatory effects of surgical trauma may impair the cavernous nerves.[9] Whereas sexual function was significantly better in the BNS than the UNS plus SNG group immediately after RP, the latter group continued to show improvement after postoperative year 2 and sexual function reached a level approximating that of bilateral nerve sparing. However, the UNS plus SNG group reported a significantly lower sexual bother score than the other 2 groups, suggesting that those who underwent RP with nerve grafting were potentially more interested or motivated to maintain or resume sexual function postoperatively. Therefore, postoperative erectile dysfunction especially within 12 months was a burden and they reported lower sexual bother scores. Although our study may not be large enough to generalize whether nerve grafting actually helps men who would otherwise not achieve erections sufficient for intercourse, these findings will be helpful in counseling patients when they are weighing a decision about RP.

Unilateral nerve grafting RP is beneficial for the early recovery of postoperative urinary continence. Urinary incontinence is a concern particularly relevant to men undergoing RP because surgery more frequently negatively impacts continence than other treatment modalities, and because patients rate urinary status as one of their greatest concerns regarding HRQOL. In a multivariate analysis Eastham et al showed that unilateral nerve preservation was associated with less postoperative incontinence than bilateral NVB resection.[10] Our study revealed that although the BNS group showed better urinary function than the UNS plus SNG group at 1 month after RP, there were no differences at 3 months and both groups improved at comparable rates after 6 months. The precise mechanism behind the functional relationship between nerve sparing and continence remains elusive, and it is most likely multifactorial. NVB preservation may influence continence not only by maintaining efferent but also afferent innervation. The effect of autonomic innervation on the sphincter mechanism was convincingly shown by intraoperative stimulation of NVBs during RP.[11] Singh et al demonstrated that patients who underwent RP with UNS plus SNG had a greater rate of urinary function recovery relative to patients in whom an SNG interposition was not performed, which was similar to our finding.[12] Other factors that may influence urinary function include the surgical methods of bladder neck reconstruction and anastomosis.[10] The current study minimized the confounding influence of surgical technique on urinary function. All patients in this study had the bladder neck reconstructed and anastomosis performed using the same technique.

Precise visualization and localization of the NVBs are often problematic during RP because of the variation in anatomical location of the cavernous nerves as well as poor exposure due to the ubiquitous presence of overlying tissues and blood during the procedure. Several studies reported that macroanatomical and electrophysiological assessments of nerve preservation showed different outcomes. The intraoperative electrophysiological assessment revealed that approximately 20% of the macroanatomical assessments were incorrect.[4] Thus, if only macroanatomical assessment was used we could not know the real impact of unilateral sural nerve interposition. With regard to the intraoperative electrophysiological test, Holzbeierlein et al claimed that responses to NVB using the CaverMap® nerve stimulator did not correlate with the precise anatomical location of the cavernous nerves as a consequence of anesthesia, medications or surgical manipulation.[13] There was a high false-negative rate reported in the CaverMap system, possibly because it measured penile tumescence. However, the most important characteristic of our system was that it measured intracavernous pressure. Kurokawa et al showed that there was no false-negative rate in this system, and that intracavernous pressure was not influenced by preoperative potency, type of anesthesia or neoadjuvant hormone therapy, suggesting high system accuracy.[6] Moreover, we revealed that nerve preservation confirmed by the system effectively predicted the recovery of potency.[14] Another important aspect of the electrophysiological assessment of NVB preservation is that the method could provide immediate feedback to surgeons during the operation. Despite attempts at direct visualization and the electrophysiological assessment of NVB, whether the preserved nerves will be functionally normal or whether vascular damage will affect continence or potency currently cannot be predicted at the time of surgery.[15] Thus, success or failure of the nerve sparing procedure is recognized 1 or 2 years after the surgery. Using the method described here a surgeon could immediately know the results of the nerve sparing procedure. This early feedback may further contribute to the improvement of the surgical outcome by the surgeon.

This prospective observational study had several limitations. This group is not a random sample and might not be representative of all men with prostate cancer who choose RP. For instance, patients electing to undergo SNG interposition may have been more motivated or surgeon technique may have changed imperceptibly with time. In addition, our study had a relatively small sample size. This poses a significant problem in the interpretation of the data because recovery of erectile function after RP depends on age as well as penile rehabilitation such that younger patients who are more motivated as seen in the nerve graft arm of this study are more likely to recover erectile function. Unfortunately our study may have insufficient power to address this issue due to the small number of patients younger than 66 years. Thus, the absence of a significant difference between the UNS+SNG group and the BNS group may be due solely to a lack of power rather than the true equivalence of these groups. We also cannot exclude RP complications such as anastomotic stricture which may impact the issue of urinary continence, although in our series the incidence was low at less than 5%. Finally, we did not distinguish those patients who use erectile aids such as phosphodiesterase type 5 inhibitors after RP. Although there is currently no consensus

regarding the implementation of penile rehabilitation programs, the initiation time, the frequency of application, the type of vasoactive agent and the dose regimen, a number of recent studies have reported on various approaches.[16,17] These factors may be a significant predictor of sexual function recovery. Despite these limitations our findings have important implications for men choosing RP for localized prostate cancer, and need to be validated in a multicenter and randomized trial.

CONCLUSIONS

These data demonstrate that in patients who underwent RP with a nerve sparing procedure, SNG interposition is associated with greater rates of postoperative sexual and urinary function. Therefore, if NVB resection is considered, SNG interposition represents an important option that may profoundly impact patient HRQOL.

Abbreviations and Acronyms

BNS	=	bilateral nerve sparing
HRQOL	=	health related quality of life
NVB	=	neurovascular bundle
PSA	=	prostate specific antigen
RP	=	radical retropubic prostatectomy
SNG	=	sural nerve graft
UCLA PCI	=	UCLA Prostate Cancer Index
UNS	=	unilateral nerve sparing

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EDITORIAL COMMENT

Enormous enthusiasm exists at present to apply cavernous nerve graft reconstruction to facilitate erectile function recovery in patients undergoing radical prostatectomy and other pelvic surgeries.[1,2] Clinical reports do indicate the feasibility of this intervention and its seemingly low morbidity. A concern is whether cavernous nerve grafting is demonstrably effective. This report does represent a fairly rigorous evaluation. The longitudinal natural history as well as the use of validated instruments are strengths. However, like other reports on this subject this study has limitations which may bias conclusions. These include lack of randomization, patient selection bias, small sample size and potential nonuniform use of erectile aids. Further study applying prospective data accrual, randomization of equally characterized, preoperatively potent patients to nerve grafting and nonnerve grafting arms of treatment, application of validated assessment tools, and sufficient clinical followup are needed for results to be conclusive.

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Sexual Function Reported by Japanese and American Men

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Purpose: We performed a cross-cultural comparison of sexual function and bother in men with localized prostate cancer in the United States and Japan.

Materials and Methods: A total of 447 Japanese and 427 American men with clinically localized prostate cancer were enrolled in separate studies of health related quality of life outcomes. Sexual function and bother were estimated before treatment with validated English and Japanese versions of the UCLA Prostate Cancer Index.

Results: Japanese men were more likely than American men to report poor sexual desire (OR 21.2, 95% CI 12.2–37.0), poor erection ability (OR 16.2, 95% CI 9.7–27.1), poor overall ability to function sexually (OR 16.7, 95% CI 9.7–28.9), poor ability to attain orgasm (OR 1.7, 95% CI 1.3–2.3), poor quality of erections (OR 2.5, 95% CI 1.9–3.5), infrequency of sexual erections (OR 2.3, 95% CI 1.7–3.1), infrequency of morning erections (OR 2.7, 95% CI 1.8–4.2) and intercourse in the previous 4 weeks (OR 2.7, 95% CI 1.9–3.8). However, Japanese men were less likely than American men to be bothered by sexual function (OR 0.36, 95% CI 0.24–0.54). A small subset of 10 Japanese-American men reported sexual function that more closely resembled their counterparts in Japan than in the United States.

Conclusions: We posit that cultural disparities in completing the quality of life surveys explain the differences in sexual activity profiles in Japanese and American men with prostate cancer.

Key Words: prostate, impotence, prostatic neoplasms, quality of life, cross-cultural comparison

Traditional definitions of the success of prostate cancer therapy have focused primarily on overall and disease-free survival, and biochemical recurrence as evidenced by PSA. Given the favorable survival outcomes associated with stage migration in recent years, patients often select primary therapy based on QOL considerations.[1] Because most men with prostate cancer are asymptomatic, it is not surprising that they are often unprepared for the diagnosis and difficult treatment decisions that they face. As treatment goals have widened to include not only survival, but also better QOL, a body of research has grown on sexual outcomes after various treatment modalities.[2,3]

Sexual function is broadly defined to include the quality and frequency of erections, strength of libido, and ability to be physically and sexually intimate, while sexual bother refers to the degree of interference or annoyance caused by any limitations in sexual function. Sexual behavior can be influenced by physiological as well as psychological or sociocultural factors.[4,5] Nonetheless, ED, which is the most common long-term side effect of prostate cancer treatment, significantly affects marital relationships.[6] Several cross-national surveys suggest that ED is more prevalent in Japanese men than in men of other countries, suggesting cultural differences in the perception and/or reporting of sexual function and associated distress.[7] However, no plausible biological explanation has been put forward.

As such, we wondered whether cross-national variations in sexual function reflect differences in the psychometric properties of the instruments rather than actual functional differences. Such a finding would have important implications for international studies that rely on instruments believed to be valid in different languages. To illuminate this issue we examined differences in self-reported sexual function and bother between American and Japanese men with newly diagnosed prostate cancer before receiving primary treatment.

MATERIALS AND METHODS

Subjects

Between 2002 and 2004, 447 Japanese men with newly diagnosed prostate cancer (cT1–T3N0M0) were enrolled in a longitudinal outcomes study. The men were treated at Tohoku University Hospital and at 2 affiliated hospitals, Kitazato University Hospital and Kurashiki Central Hospital. Between 1999 and 2003, 427 American men with localized prostate cancer (cT1–T3N0M0) who were treated with radical prostatectomy or brachytherapy at UCLA were enrolled in a separate longitudinal outcomes study. All recruitment and study protocols were approved by the institutional review boards at the respective institutions.

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Study received approval from the institutional review boards at the respective institutions.

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Outcome Measures

Sexual function and sexual bother (distress from sexual dysfunction) were measured separately with the UCLA PCI.[8] Each UCLA PCI domain is scored from 0 to 100 points with higher scores representing better outcomes. Hence, a higher sexual function score indicates better function and a higher sexual bother score indicates less bother. On the UCLA PCI sexual function is measured by 8 items and sexual bother is measured by a single item. UCLA PCI performs well not only in men with prostate cancer, but also in healthy older man without prostate cancer[9] and in men presenting for evaluation for ED.[10] A validated Japanese version is available.[11]

Questionnaires were completed at home within the month before surgery and returned in postage prepaid envelopes. All men were aware of the cancer diagnosis before completing the questionnaire. Comorbidities were documented using a patient reported checklist at baseline, while clinical variables were abstracted from medical records.

Statistical Analysis

Descriptive statistics are presented for demographic and clinical characteristics. We dichotomized the response to each item, grouping the best and worst outcomes (see Appendix). We used the chi-square test to compare the 9 items between Japanese and American men. We also performed logistic regression for each item with country as our main predictor variable, adjusting for each subject age with $p < 0.05$ considered statistically significant. All statistical analyses were performed with SAS® 9.1.

TABLE 1. *Sample characteristics*

	Japanese		American		p Value
No. pts	412		427		
Age at survey:					<0.001
Mean ± SD	67.2 ± 5.5		62.1 ± 7.9		
Median (range)	67 (47–81)		62 (40–83)		
PSA at diagnosis (ng/ml):					
Mean ± SD	8.7 ± 5.9		8.0 ± 9.0		0.194
Median (range)	7.1 (1.3–54)		6 (0.02–120)		
No. clinical stage (%):					<0.001
T1	239	(58)	305	(71)	
T2	148	(36)	117	(28)	
T3	25	(6)	5	(1)	
No. initial treatment (%):					0.001
Radical prostatectomy	350	(85)	325	(76)	
Brachytherapy	62	(15)	102	(24)	
No. biopsy Gleason sum (%):					<0.001
6 or Less	171	(42)	303	(71)	
7 or Greater	241	(58)	121	(28)	
Unknown	—		3	(1)	
No. comorbidity count (%):*					0.002
0	152	(37)	157	(37)	
1	113	(27)	156	(37)	
2	77	(19)	70	(16)	
3 or Greater	70	(17)	42	(10)	
Unknown	—		2	(0)	
No. ethnicity (%):					—
White	—		352	(82)	
Black	—		14	(3)	
Hispanic	—		13	(3)	
Asian	412	(100)	18	(4)	
Multiracial	—		5	(1)	
Other	—		24	(6)	

* Including hypertension, stomach, intestinal and gastrointestinal diseases, heart disease, cancer other than prostate cancer, lung disease, diabetes, stroke and blood disease.

RESULTS

Surveys were received from 412 Japanese and 427 American men. None of the men received androgen ablation before completing the questionnaire. The American men were younger and had earlier stage and lower grade tumors ($p < 0.001$, table 1). The groups did not differ in mean prebiopsy PSA.

Even after controlling for age the Japanese men were much more likely than American men to report low sexual desire (OR 21.2, 95% CI 12.2–37.0), poor erections (OR 16.2, 95% CI 9.7–27.1) and poor overall sexual function (OR 16.7, 95% CI 9.7–28.9). The Japanese men were more likely to report difficulty with orgasms (OR 1.7, 95% CI 1.3–2.3), and low quality (OR 2.5, 95% CI 1.9–3.5) and frequency (OR 2.3, 95% CI 1.7–3.1) of erections. The Japanese men were more likely to report not having morning erections (OR 2.7, 95% CI 1.8–4.2) and report having achieved no intercourse in the previous 4 weeks (OR 2.7, 95% CI 1.9–3.8). However, despite reporting worse sexual function for all 8 items the Japanese men were significantly less likely to report sexual bother (OR 0.36, 95% CI 0.24–0.54, table 2). When analysis was limited to men 60 years or younger in the 2 ethnic groups, the differences persisted for sexual function (items 1 to 8) but not for sexual bother (item 9).

Of the American cohort 18 men were Asian, including 10 who were identified by their surnames as Japanese-Americans. We performed an exploratory ad hoc analysis in these 10 Japanese-American men to identify potential acculturation effects. Nine of the 10 Japanese-American men reported that sexual desire, erection ability, orgasm and awakening with an erection were fair, poor or very poor. Furthermore, all 10 men reported that overall sexual function ability was poor or very poor. Six of the 10 men considered that the quality and frequency of erections were poor or very poor. Only 2 of the 10 men reported having achieved intercourse more than once during the previous 4 weeks. The Japanese-American men reported dysfunction at rates closely approximating those of the native Japanese men but these 10 men reported almost twice as much distress from sexual function as the Japanese men (60% vs 36%).

DISCUSSION

Our study has several important findings. 1) We found different cultural profiles of sexual function in Japanese and American men with localized prostate cancer. Using a self-reported questionnaire Japanese men reported less sexual activity than American men even after adjusting for age. This finding is consistent with other reports, in which ED and decreased libido were noted in a greater proportion of Japanese than American men.[12] Population based data from Japan indicate that the proportion of ED is 20%, 42% and 64% for ages 50 to 59, 60 to 69 and 70 to 79 years, respectively, which are higher than in other countries.[4,13] The relationship between sexual function and serum testosterone is controversial. However, in the Japanese male population no continuous decrease in testosterone has been noted after age 40 years, as it has in other countries.[14]

In Japan physician consultation time at outpatient clinics is much shorter than in the United States. Moreover, the condition of the clinical setting at Japanese hospitals may decrease patient motivation. Some patients are asked to

TABLE 2. *Men reporting poor sexual function by ethnicity*

Question No.	Question	% Japanese (No.)	% American (No.)*	OR (95% CI)
		412	427	
1	Sexual desire level	96 (394)	51 (214)	21.2 (12.2–37.0)
2	Ability to achieve erection	95 (386)	49 (204)	16.2 (9.7–27.1)
3	Ability to achieve orgasm	62 (246)	40 (167)	1.7 (1.3–2.3)
4	Erection quality	64 (258)	33 (137)	2.5 (1.9–3.5)
5	Erection frequency	61 (246)	32 (135)	2.3 (1.7–3.1)
6	Awakened with erection	91 (367)	72 (303)	2.7 (1.8–4.2)
7	Intercourse	83 (335)	56 (238)	2.7 (1.9–3.8)
8	Overall sexual function ability	96 (387)	52 (216)	16.7 (9.7–28.9)
9	Sexual function problem	11 (47)	25 (97)	0.36 (0.24–0.54)

All models were controlled for patient age.
* Referent.

wait outside the consultation room but they can overhear conversations between the doctor and other patients, which may in turn cause them to be self-conscious about discussing sensitive issues with the physician during their own consultations. These factors in the clinical setting discourage patients from raising complicated psychological issues, such as sensitive sexual aspects of treatment, and force them to focus on the general physical aspects. A safer and more private atmosphere might encourage more open dialogue about sexual function. Nonetheless, it would be valuable to distinguish between patients who do not put a high priority on sexual function and those who are hesitant to raise the topic with their medical providers. Conversely while male erectile rigidity contributes to the frequency of sexual intercourse, it is not necessarily associated with a satisfactory sexual life in the partners of Japanese men.[15] The discrepancy between the responses of Japanese males and their partners might be explained by discordant views of what represents a satisfactory sexual life, eg noncoital intimate activities. That the lack of privacy during consultations inhibits frank personal discussions may also limit candor in written self-reported sexual function.

2) Although Japanese men reported less sexual activity than American men, Japanese men were less likely to be bothered. Other studies show that, unlike their American counterparts, older Japanese men do not report dissatisfaction with sexual life.[11] The pattern of help seeking behaviors differs substantially between Japan and the United States. In Japan most men take no action, while in America men may seek help from the partner, family members or other sources of social support. Of those who do not seek treatment younger men seem to believe that ED would resolve spontaneously, while older men resist seeking treatment because they believe that ED is a natural part of aging.[14]

Although Japanese beliefs regarding sexual dysfunction have changed considerably in recent years, discussion of sexually related topics continues to be repressed in Japanese patient-physician encounters. In fact, the most commonly cited reason for not self-referring to a doctor is that sexual problems are not medical problems.[16] In Japan it may be difficult to find medical professionals who consider it their role to deal with the sexual issues of a patient. Hence, in addition to improving privacy during consultations, it is also important that providers be trained more comprehensively in male health. This added emphasis would focus greater attention on the sexual concerns of cancer survivors, especially given the recent pharmacological advances in this discipline.

Conversely American men tend to perceive sexual difficulties as a serious medical issue that requires intervention. This is consistent with other reports documenting the great weight that sexual dysfunction carries with many American men.[2,4] Being married or living with a partner might motivate American men to seek treatment for ED, which caused more distress due to decreased function.

Although our Japanese-American sample was too small for statistical analyses, several observations in this group are noteworthy and hypothesis generating. In particular the patterns of sexual function reported by Japanese-American men were remarkably similar to those reported by Japanese men. This is consistent with the relatively low reported rates of sexual assertiveness in Asian countries.[17] Contributing to this lower reported sexuality are Asian cultural restraints on sexual behavior. This suggests that cultural factors and deeply embedded health beliefs may have a decisive role in defining health seeking behaviors for sexual problems. However, to our knowledge there have been no empirical investigations of the specific role of culture in Japanese-American men. However, despite similar sexual function Japanese-American men in our sample showed a trend toward more sexual bother than their Japanese counterparts. The reason for this discrepancy is unclear but it may be related to the natural evolution of cultural norms in immigrant communities. The Japanese-American men may have perceived sexual dysfunction more as a medical issue than did their peers in Japan.[17] Future research is needed to investigate the cultural and structural causes of this variation.

There are several important limitations to this study. 1) This group is not a random sample and it might not be representative of all men with newly diagnosed early prostate cancer. Selection bias may have been introduced by including individuals who were more interested in the topic or had more time to answer the questions. Moreover, the groups were not well balanced in several domains, such as age, treatment type and comorbidity. 2) We did not distinguish men who may have used erectile aids, such as type 5-phosphodiesterase inhibitors or vacuum devices. These factors may limit the generalizability of our findings. 3) Health related QOL and patient satisfaction may depend in part on factors such as the content of counseling, which are more difficult to measure. 4) Because we assessed outcomes after the cancer diagnosis, sexual function and bother outcomes may have been affected even before treatment. However, other investigators using the UCLA PCI noted no differences in sexual domain scores before

and after diagnosis.[18] 5) The lack of objective data, such as serum testosterone and audiovisual sexual stimulation tests, was inherent in our study design.

Despite these limitations to our knowledge this cross-national survey is the first to document such differences in a prostate cancer population. It may increase physician awareness and understanding of sexual health issues, and help them encourage patients to identify and overcome potential barriers to discussing and seeking help for sexual dysfunction. Different cultures have different concepts of health, including sexuality, well-being, illness and disease. Even using validated survey instruments we must be aware that multicultural issues may result in significant bias in data collection. Further research is required to understand fully which factors are most important in the individual ethnicities.

CONCLUSIONS

In patient reported questionnaires Japanese men with localized prostate cancer report worse sexual function and less bother from the decreased function than American men. Cultural differences appear to have an important role in the reporting of sexual activity and the perception of related distress. In the absence of an underlying biological explanation for cross-national differences in sexual function we suspect that cultural differences in how the QOL surveys were interpreted may explain the differences in sexual activity profiles in Japanese and American men with prostate cancer.

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APPENDIX

Definitions of Poor Sexual Function

1. Your level of sexual desire?
   Very poor/poor/fair vs good/very good
2. Your ability to have an erection?
   Very poor/poor/fair vs good/very good
3. Your ability to reach orgasm (climax)?
   Very poor/poor/fair vs good/very good
4. How would you describe the usual QUALITY of your erection?
   None at all/not firm enough for any sexual activity/firm enough for masturbation or foreplay only vs firm enough for intercourse
5. How would you describe the FREQUENCY of your erections?
   Never/less than half/about half the time I wanted vs more than half the time I wanted/whenever I wanted
6. How often have you awakened in the morning or night with an erection?
   Never/seldom (less than 25% of the time)/not often (less than half the time) vs often (more than half the time)/very often (more than 75% of the time)
7. During the last 4 weeks did you have vaginal or anal intercourse?
   No/once vs more than once
8. Overall, how would you rate your ability to function sexually during the last 4 weeks?
   Very poor/poor/fair vs good/very good
9. Overall, how big a problem has getting and maintaining an erection been for you during the last 4 weeks?
   Big problem/moderate problem vs small problem/very small problem/no problem

Abbreviations and Acronyms

ED = erectile dysfunction
PSA = prostate specific antigen
QOL = quality of life

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Postoperative Inguinal Hernia After Radical Prostatectomy for Prostate Cancer

Takashige Abe, Nobuo Shinohara, Toru Harabayashi, Ataru Sazawa, Shin Suzuki, You Kawarada, and Katsuya Nonomura

OBJECTIVES To determine the incidence of inguinal hernia after radical prostatectomy and compare it with the incidence in patients with prostate cancer treated with radiotherapy. We also analyzed the effect of potential risk factors for inguinal hernia after radical prostatectomy.

METHODS We investigated the medical records of 53, 43, and 74 men who underwent open radical retropubic prostatectomy (RRP), laparoscopic radical prostatectomy (LRP), or radiotherapy with or without laparoscopic pelvic lymph node dissection, respectively, and evaluated the respective incidence of inguinal hernia after these therapies. The risk factors were analyzed using a Cox proportional hazards model.

RESULTS The incidence of inguinal hernia was 17% (9 of 53), 14.0% (6 of 43), and 1.4% (1 of 74) in open RRP, LRP, and radiotherapy groups, respectively. Multivariate Cox proportional hazards analysis demonstrated that open RRP and LRP were significant risk factors for the development of inguinal hernia.

CONCLUSIONS Urologists should be aware that inguinal hernia is an important postoperative complication of open RRP. More interestingly, even LRP could promote the development of postoperative inguinal hernia. UROLOGY 69: 326–329, 2007. © 2007 Elsevier Inc.

Because of the increasing use of prostate-specific antigen (PSA) testing and subsequent stage migration toward more organ-confined disease, the number of patients who undergo radical retropubic prostatectomy (RRP) has increased tremendously in the past decade.[1,2] The side effects of urinary incontinence and erectile dysfunction are well documented. In 1996, Regan and coworkers[3] reported that 12% of 92 patients treated with RRP developed an inguinal hernia approximately 6 months postoperatively. Subsequently, additional studies have reported that inguinal hernia is a frequent complication after RRP.[4–8] Nevertheless, this problem has not received much attention because inguinal hernias frequently occur in men aged 50 to 70 years and are regarded as a primary event, not secondary to RRP.

To clarify the clinical significance of inguinal hernia as a postoperative complication of RRP, we evaluated the incidence of inguinal hernia after open RRP in our recent series and compared it with the incidence in patients with prostate cancer treated by radiotherapy with or without laparoscopic pelvic lymph node dissection during the same period. In addition, we have performed laparoscopic radical prostatectomy (LRP) at our institution since June 2000, and these patients were also evaluated to determine the incidence of postoperative inguinal hernia.

MATERIAL AND METHODS

We retrospectively reviewed a total of 170 male patients with prostate cancer who underwent open RRP, LRP, or radiotherapy at our institution from January 2000 to March 2005. RRP with bilateral pelvic lymph node dissection was performed through a lower midline incision extending from the pubis to the umbilicus in 53 patients according to a modification of the Walsh technique.[9] LRP was performed in 43 patients. Of these, 13 patients simultaneously underwent laparoscopic pelvic lymph node dissection. Initially, we used the transperitoneal approach according to the Montsouris technique[10] in 25 patients. Subsequently, we used the extraperitoneal approach in 18 patients. The specimen was placed in a laparoscopic bag and removed by way of the umbilical port incision. The incision was extended as needed. Four patients required open conversion because of ureteral injury in one, rectal injury in one, massive bleeding in one, and severe subcutaneous emphysema in one. Of the 170 patients, 74 underwent radiotherapy. Radiotherapy alone was performed in 44 patients and radiotherapy with laparoscopic pelvic lymph node dissection was performed in 30 patients, according to the pretreatment PSA level, clinical stage, and Gleason grade.

Almost all patients were followed up at 3-month intervals at our institution; a few patients underwent follow-up at our affiliated hospitals using the same protocol. At each visit, the serum PSA level was measured, and the patients were actively

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Table 1. Patient characteristics

Characteristic	Open RRP (n = 53)	LRP (n = 43)	Radiotherapy (n = 74)	
			No LPLND (n = 44)	LPLND (n = 30)
Age (yr)	68.8 ± 5.4	64.4 ± 6.5*	68.3 ± 7.2	68.7 ± 7.7
PSA (ng/mL)	11.9 ± 8.5	9.6 ± 5.8	13.6 ± 14.4	26.8 ± 20.1*
BMI (kg/m^2)	23.6 ± 2.8	23.8 ± 2.7	24.2 ± 3.5	23.9 ± 2.4
Follow-up time (mo)	27.3 ± 14.9	31.1 ± 19.0	32.3 ± 17	24.1 ± 15.2
Previous abdominal surgery (hernia repair)	19 (1)	16 (1)	17 (2)	17 (2)
Postoperative urethral stricture	2	6	—	—
Operative time (min)				
Median	240	346	—	—
Range	121–360	214–824*		
Blood loss (mL)				
Median	1110	1190	—	—
Range	350–3825	300–9900		

RRP = radical retropubic prostatectomy; LRP = laparoscopic radical prostatectomy; LPLND = laparoscopic pelvic lymph node dissection; PSA = prostate-specific antigen; BMI = body mass index.
Data presented as mean ± SD or number, with percentages in parentheses, unless otherwise noted.
* $P < 0.05$

asked whether any new medical problem had developed since their last visit. A physical examination was not routinely performed. Endoscopy was performed if the patient reported narrowing of the urine stream or other signs of bladder neck stricture. The patient records were reviewed, and the occurrence of inguinal hernia after treatment for prostate cancer was evaluated. The obtained data were age, pretreatment PSA level, Gleason grade, stage, body mass index, and a history of the previous abdominal surgery, including inguinal hernia. In the RRP and LRP groups, the operative time, blood loss, and incidence of postoperative urethral stricture were analyzed. Postoperative urethral stricture was diagnosed endoscopically as significant when endoscopy at the anastomotic portion indicated the need for intervention.

In patients in whom a postprostatectomy inguinal hernia was repaired surgically, the surgical record was reviewed to determine the hernia type (direct or indirect) and laterality (left or right side).

The differences between the groups were compared using the Mann-Whitney U test and Fisher's exact test. The hernia-free rate was estimated by the Kaplan-Meier method, and the differences among groups were tested using the log-rank test. Cox proportional hazard analysis was used to identify the risk factors for inguinal hernia. $P < 0.05$ was considered significant.

RESULTS

The patient characteristics are listed in Table 1. The mean age in the LRP group was significantly younger than that of the other groups, and the mean pretreatment PSA level in the patients who underwent radiotherapy with laparoscopic pelvic lymph node dissection was significantly greater than those in the other groups. During follow-up, inguinal hernia occurred in 9 (17%) of 53 patients in the RRP group. In addition, we observed the development of inguinal hernia in 6 (14%) of the 43 patients who underwent LRP; 5 patients developed hernia after the transperitoneal approach and 1 after the extraperitoneal approach. The median interval until the hernia diagnosis was 11 months (range 6 to 52) after RRP and 16.5 months (range 6 to 36) after LRP. In the RRP group and LRP group, 7 (77.8%) of 9 patients and 4 (66.7%) of 6 patients, respectively, developed an inguinal hernia within 2 years postoperatively. In the radiotherapy group, 1 patient who did not undergo laparoscopic pelvic lymph node dissection developed an inguinal hernia 23 months after therapy. The hernia-free rates were significantly lower after open RRP and LRP than after radiotherapy (Fig. 1).

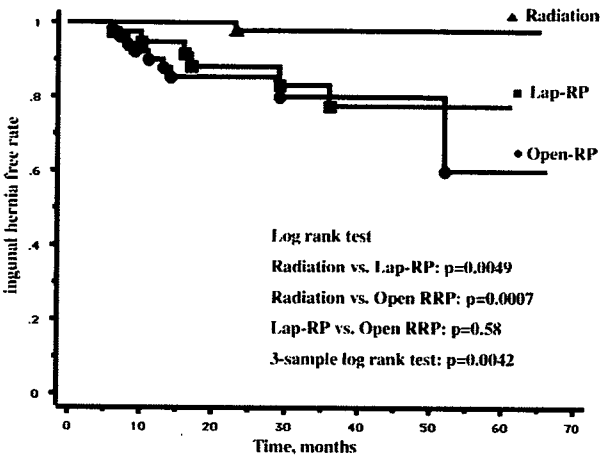

Figure 1. Kaplan-Meier plot comparing cumulative hernia-free survival in open RRP, LRP (Lap-RP), and radiotherapy groups.

Table 2 shows the type and laterality of the inguinal hernias. Of the 16 patients with inguinal hernia, 11 (69%) were indirect, 1 (6%) was direct, and 4 (25%) were unknown. We found right-side dominance in the RRP group. Of the 9 patients, 8 developed inguinal hernia on the right side and 1 bilaterally.

Table 3 shows the results of multivariate analysis in all patients. RRP and LRP were significant risk factors for postoperative inguinal hernia compared with radiotherapy. Other characteristics were not significant. In addition, we did not find any significant difference between

Table 2. Type and laterality of inguinal hernia

	Open RRP (n = 9)	LRP (n = 6)	Radiotherapy (n = 1)
Type (n)			
Indirect	7	4	0
Direct	0	1	0
Unknown	2	1	1
Laterality (n)			
Right	8	2	0
Left	0	4	0
Bilateral	1	0	1

Abbreviations as in Table 1.

the hernia group and nonhernia group with regard to a previous history of inguinal hernia, postoperative urethral stricture incidence, blood loss, and operative time in the two prostatectomy groups.

COMMENT

In the present study, we observed a 17% incidence of inguinal hernia after open RRP, significantly greater than that after radiotherapy. This result was compatible with the 8.6% to 21% incidence previously reported.[3–8] It was also consistent with earlier reports that most hernias occurred within the first 24 months postoperatively and that indirect hernia was predominant.[3,4,6–8] Because multivariate analysis using a Cox proportional hazards model showed that RRP was a significant risk factor for inguinal hernia, we should keep in mind that inguinal hernia is a postoperative complication of RRP, but not part of the natural history. In addition, we noted a 14% rate of inguinal hernia after LRP, which was also significantly greater than that after radiotherapy. To our knowledge, this is the first report describing postoperative inguinal hernia after LRP.

Several clinical factors have been reported to be associated with the development of postoperative inguinal hernia. Increasing age,[6] body mass index less than 23 kg/m^2,[4] previous history of inguinal hernia,[4,6,7] and wound-related problems[7] have been shown to be significant risk factors, although conflicting results have been reported regarding the influence of postoperative anastomotic stricture.[4,6,7] Any abdominal surgery, even appendectomy, tends to weaken the abdominal wall and predispose toward the occurrence of an inguinal hernia.[11] In our study, multivariate Cox proportional analysis showed that previous abdominal surgery, age older than 70 years, and body mass index (greater than 23 kg/m^2) were not risk factors for inguinal hernia after definitive therapy for prostate cancer. Radical prostatectomy, whether open or laparoscopic, was a significant risk factor. Furthermore, we compared the previous history of inguinal hernia, urethral stricture, blood loss, and operative time between patients with and without postoperative inguinal hernia in the open RRP and LRP groups and could not identify any potential risk factors. However, a previous history of inguinal hernia might not have been sufficiently analyzed because only 2 patients in two prostatectomy groups had a history of inguinal hernia in the present study.

Since Guillonneau and Vallancien[12] presented their promising early results of LRP, the procedure has been gaining increasing acceptance by many urologists and patients owing to reports describing successful series that have demonstrated lower blood loss/transfusion rates with apparently equivalent outcomes. In our institution, 43 patients underwent LRP, and we observed a 14% incidence of hernia in the LRP group. None of the patients developed an inguinal hernia after radiotherapy with laparoscopic pelvic lymph node dissection. Although inguinal hernia occurred more often after the transperitoneal approach than after the extraperitoneal approach, the influence of approach could not be analyzed because of the significant difference in the follow-up period (median follow-up time 40.4 months in the transperitoneal approach group and 18.3 months in the extraperitoneal approach group). As described, we did not find any previous report examining the incidence of inguinal hernia after LRP. However, our experience may not be universal, because the operative time was longer in our series than that in large centers,[13,14] and our skill in LRP is still progressing. Although it is possible that inguinal hernia may have had a greater tendency in this selected series, we consider our results interesting and that inguinal hernia is a potential postoperative complication even after LRP.

In a prospective study to define the incidence of subclinical inguinal hernia, Nielsen and Walsh[15] recently reported that 33% of the 430 patients who underwent RRP had an incidental inguinal hernia that was repaired during RRP with a patch of mesh for direct hernia or with 2-0 Prolene figure-of-eight suture approximating the iliopubic tract to the transverse arch for indirect hernia. They concluded that incidental inguinal hernias were commonly found and that preperitoneal hernia repair was readily accessible to urologists. In addition, a laparoscopic study demonstrated a 13% incidence of subclinical inguinal hernia,[16] and a 20% incidence of internal ring defect was found in a cadaveric study.[17] Therefore, it might be a reasonable theory that postoperative hernias represent the prevalence of subclinical hernias that become clinically manifest after surgery, rather than a new onset. It is also possible that preexisting subclinical hernias could progress to postoperative inguinal hernias in some patients. Attention must be paid to detecting subclinical inguinal hernias intraoperatively. Injury of the transversalis fascia is also one of the potential mechanisms, because this injury will induce failure of the so-called shutter mechanism produced by the transverse aponeurotic arch when the transverse abdominal muscle and internal oblique muscles are stretched. However, this is not a sufficient explanation of the mechanism involved in inguinal hernia development, because the incidence of inguinal hernia after RRP was almost equal to that after LRP. Stretch injury of the groin region by retraction of

Table 3. Cox proportional hazards ratio of inguinal hernia

Factor	Patients (n)	Hazard Ratio (95% CI)	P Value
Previous abdominal surgery			
No	101	1	
Yes	69	0.93 (0.33–2.59)	0.89
Body mass index (kg/m^2)			
≥23	108	1	
<23	62	1.60 (0.57–4.59)	0.38
Age (yr)			
≤70	95	1	
>70	75	1.78 (0.62–5.08)	0.28
Therapy			
Radiotherapy	74	1	
Open RRP	53	13.81 (1.73–110.18)	0.013
LRP	43	14.00 (1.61–121.50)	0.017

CI = confidence intervals; other abbreviations as in Table 1.

the vasa deferentia during prostatectomy is also a reasonable explanation. The right side dominance of postoperative inguinal hernia observed in the open RRP group could reflect such an injury, because the surgeon usually stands on the left side of the patient, which could result in excessive dissection in the right groin area. However, this is also not a sufficient explanation, because surgeons usually do not retract the vasa deferentia during LRP. In LRP, prolonged use of the pneumoperitoneum might cause adverse effects on the development of inguinal hernia. Although we could not explain the precise mechanism of postoperative inguinal hernia, the development of inguinal hernia is likely induced by several of the factors described above.

Because our study was retrospective, it is possible that some hernias were missed on the preoperative physical examination, as well as intraoperatively. However, we have concluded that inguinal hernia is an important and unacceptable complication in patients who have undergone RRP and, even, those treated with LRP. Although often asymptomatic, an inguinal hernia can cause significant pain and discomfort. Because emergency surgery for a strangulated hernia is associated with a 14% mortality rate,[18] we consider screening for inguinal hernias, both before and after radical prostatectomy, important. Additional studies are warranted to define the causal mechanisms, as well as prophylactic procedures.

CONCLUSIONS

Urologists should be aware that inguinal hernia is an important postoperative complication of RRP. Also, even LRP might promote the development of postoperative inguinal hernia.

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Prostate-Specific Antigen/Prostatic Acid Phosphatase Ratio Is Significant Prognostic Factor in Patients with Stage IV Prostate Cancer

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OBJECTIVES Novel prognostic indexes clinically applicable for patients with Stage IV prostate cancer are needed because prostate-specific antigen (PSA) tests occasionally fail to reflect the prognostic outcome. We investigated various clinicopathologic parameters in men with Stage IV prostate cancer and evaluated the utility of the PSA/prostatic acid phosphatase (PAP) ratio as a prognostic index.

METHODS We reviewed 241 patients with Stage IV prostate cancer, who were treated in Niigata Cancer Center Hospital from 1992 to 2004. Survival curves were generated using the Kaplan-Meier method. Univariate and multivariate analyses of survival associations, including age, performance status, clinical presentation, disease localization, pathologic findings, and serologic markers, were conducted using the log-rank test and Cox proportional hazard models.

RESULTS The 5-year overall survival rate using the Kaplan-Meier method for all 241 patients was 43.0%. No significant difference was found in the survival rates according to PSA level. However, the 5-year survival rate was significantly lower in patients with a PSA/PAP ratio of less than 3.0 ($P = 0.0022$): 24.2% and 48.0% in those with a PSA/PAP ratio of less than 3.0 and 3.0 or greater, respectively. On multivariate analysis using the proportional hazards model, the statistically significant prognostic factors of overall survival were alkaline phosphatase ($P = 0.0413$), lactate dehydrogenase ($P = 0.0409$), and the PSA/PAP ratio ($P = 0.0113$).

CONCLUSIONS The PSA/PAP ratio is a valuable prognostic indicator in men with Stage IV prostate cancer. Although our study found that other laboratory tests also had a prognostic influence, the PSA/PAP ratio was an essential index implicated in the physiopathology of prostate cancer. UROLOGY 70: 702–705, 2007. © 2007 Elsevier Inc.

Prostate cancer is a major cause of cancer-related deaths in many countries worldwide.[1,2] The incidence of prostate cancer is high in the United States and Europe, and the incidence has been rapidly increasing in Asian populations for the past 20 years.[3,4] Recent advances in screening and diagnostic techniques have resulted in the detection of prostate cancer at earlier stages. However, a fraction of patients still present with metastatic conditions, and their management is a serious social and medical problem.

Therapeutic options vary according to the primary disease stage in prostate cancer. Patients with localized disease may be treated with radical surgery or radiotherapy, and those with locally advanced disease are likely to be treated with combined modalities.[5] In metastatic disease, in contrast, androgen deprivation is the therapeutic standard, and the treatment of patients with such disease is frequently only palliative. Most patients with metastatic prostate cancer initially respond to androgen-deprivation therapy, but almost all cases eventually progress to hormone-independent cancer. Additional therapeutic options are therefore warranted for patients with advanced prostate cancer in the initial therapeutic planning. Moreover, it is important to estimate the prognosis for each case and consider alternate therapy (ie, primary chemoendocrine therapy) for high-risk patients.[6] Accordingly, extended knowledge regarding the prognostic factors is essential for the design of future studies.

Many prognostic factors for advanced prostate cancer have been established. Several investigators have reported on the association between survival and clinicopathologic parameters, including serum lactate dehydrogenase, alkaline phosphatase, blood hemoglobin, Gleason score, and performance status in men with metastasized prostate cancer.[7–11] In particular, prostate-associated tumor markers have

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been investigated to find promising serologic values that more directly and accurately reflect the disease extent and prognosis. Prostate-specific antigen (PSA) is a well-known, useful tumor marker of prostate cancer and is also valuable as a prognostic factor. Although the PSA levels reflect changes resulting from cancer and also those due to inflammation or benign proliferation,[12] a significantly high PSA level usually suggests advanced prostate cancer.[13] However, urologists occasionally encounter patients with prostate cancer with advanced disease stages and relatively low PSA levels. This paradoxical phenomenon can be explained as follows: PSA is produced in normal epithelial cells in the prostatic glands, ducts, and well-differentiated prostate adenocarcinoma, but its expression is potentially downregulated in poorly differentiated cancer cells.[14,15]

The prognosis of patients with Stage IV prostate cancer is discouraging, and their treatment is a challenging problem. It is difficult to predict in which patients treatment with primary hormonal therapy will fail. We investigated numerous clinicopathologic candidates to uncover potential prognostic factors available in clinical practice and have presented several significant indexes to predict the outcome of patients with Stage IV prostate cancer.

MATERIAL AND METHODS

Patient Characteristics

We reviewed the medical records of 287 patients with clinical Stage IV prostate cancer, who were treated at Niigata Cancer Center Hospital from January 1992 to December 2004. We excluded cases in which the pretreatment PSA level, PAP, or histologic diagnosis was not available. Data were available for 241 patients. Clinical staging was determined according to the TNM classification of the International Union Against Cancer (UICC), 1997. The clinical examinations included the PSA and PAP tests, digital rectal examination, transrectal ultrasonography, isotope bone scanning, and computed tomography.

PSA and PAP Measurement

The pretreatment serum PSA level was measured using the Markit-M assay (Dainippon Pharma, Osaka, Japan) from January 1, 1992, to August 31, 1998, and the Tandem-R assay (Hybritech, San Diego, Calif) from September 1, 1998, to December 31, 2004.[16] The Markit-M PSA value was adjusted to the Tandem-R PSA value using the regression slope between the two assays.[16]

The pretreatment serum PAP level was measured using the radioimmunoassay kits Human Prostatic Acid Phosphatase Eiken[17] (Eiken Chemical, Tokyo, Japan) from January 1, 1992, to November 30, 1998, and the LS Reagent Eiken PAP using a Full Automated CLEIA System (Eiken Chemical) from December 1, 1998, to December 31, 2004. The two PAP assays resulted in almost equal values.

Statistical Analysis

Survival curves were generated using the Kaplan-Meier method. Univariate and multivariate analyses for survival-associated parameters were conducted using Cox proportional hazard models, with $P < 0.05$ considered to indicate statistical significance.

Table 1. Patient and tumor characteristics (n = 241)

Age (yr)	
Range	48–90
Mean	72.3
PSA (ng/mL)	
Range	1.4–28,530
Median	210
PAP (ng/mL)	
Range	0.1–9,480
Median	19
Performance status	
0	133
1	77
2	19
3	11
4	1
Tumor stage	
T1	1
T2	9
T3	159
T4	72
N0	142
N1	99
M0	39
M1a	21
M1b	163
M1c	18
Stage C (T4N0M0)	20
Stage D1 (N1M0)	19
Stage D2 (M1)	221
EOD	
0	67
1	51
2	59
3	56
4	7
Unknown (≥1)	1
Tumor histologic type (dominant)	
Well	12
Moderate	126
Poor	102
Unknown	1

PSA = prostate-specific antigen; PAP = prostatic acid phosphatase; EOD = extent of disease in bone metastases.

RESULTS

Primary Clinicopathologic Features

We present the primary data on the clinical, pathologic, and treatment-related characteristics of the patients in Table 1. The median follow-up period was 31 months (range 1 to 161, mean 40.2).

Overall Survival According to PSA and PAP Tests

The 5-year overall survival rate using the Kaplan-Meier method for all 241 patients was 43.0%. No significant difference was found in the survival rates according to PSA or PAP level. However, the 5-year survival rate was significantly lower for patients with a PSA/PAP ratio of less than 3.0 ($P = 0.0022$). The rate was 24.2% and