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Original Article: Clinical Investigation

Effect of androgen deprivation therapy on quality of life in Japanese men with prostate cancer

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Objective: We evaluated health-related quality of life (HRQOL) in Japanese men receiving androgen deprivation therapy (ADT) for prostate cancer.

Methods: Fifty-six men were enrolled in this study. HRQOL was prospectively measured before ADT, and at 3, 6 and 12 months after treatment began, using a general (36-item Short-Form Health Survey) and disease-specific (the University of California, Los Angeles Prostate Cancer Index) HRQOL questionnaire.

Results: In the general HRQOL questionnaire, patients with stage B ($n = 22$) or C ($n = 17$) disease showed a decline in vitality at 6 and 12 months ($P < 0.05$ for both). Stage D patients ($n = 17$) had improvements in bodily pain at 3 and 12 months ($P < 0.05$ for both), vitality at 12 months ($P < 0.05$), role-emotional at 6 months ($P < 0.05$), and mental health at 3 months ($P < 0.05$). When clinical stages were not considered, there were no significant changes in the 36-item Short-Form Health Survey. As for the disease-specific HRQOL, urinary function improved after ADT at 6 and 12 months ($P < 0.05$ for both), and urinary bother decreased at 3 ($P < 0.05$), 6 ($P < 0.005$) and 12 months ($P < 0.05$). Sexual function decreased at 3 ($P < 0.05$), 6 ($P < 0.005$) and 12 months ($P < 0.005$) but sexual bother improved at 6 and 12 months ($P < 0.05$ for both). If patients were stratified by clinical stages, similar findings were observed.

Conclusions: General HRQOL was mostly unaffected by ADT in Japanese men. Disease-specific questions indicated an increase in urinary function. Although deterioration of sexual function was marked, most patients did not report sexual bother. Our results shed new light on the impact of ADT on HRQOL and could provide useful information about patient-centered outcome evaluations.

Key words: androgen deprivation therapy; health-related quality of life; prostate cancer.

Introduction

The incidence of prostate cancer in Japanese men is increasing, although it is still lower than that in Western countries.[1] The rising incidence in Japan has been revealed by the widespread use of the serum prostate-specific antigen (PSA) test. In recent years, use of PSA screening is believed to have contributed to an increasing number of patients being diagnosed at younger ages and at earlier stages of disease. However, many patients are still diagnosed with metastatic prostate cancer requiring androgen deprivation therapy (ADT).[2,3] In addition, ADT is sometimes prescribed for less-advanced disease, including asymptomatic cases of localized prostate cancer.[4]

In the past 10 years, there has been a rapid increase of interest in health-related quality of life (HRQOL) among patients with prostate cancer. It is now widely accepted that the impact of ADT on HRQOL should be part of the clinical decision-making process, because the survival rate for patients is not the only factor that affects their treatment choice. For example, a treatment that has a lower survival rate might be preferred to one with a higher survival rate if the former can confer a higher quality of life. Accordingly, HRQOL studies can provide important information for patients and clinicians.

Several tools have been developed to evaluate quality of life. These tools are multidimensional and cover physical, psychosocial, and emotional status, as well as patient autonomy, and are applicable to various medical conditions. A generic measuring instrument, the 36-item Short-Form Health Survey (SF-36), is used extensively throughout the world.[5,6] In terms of disease-specific quality of life concerns, the University of California Los Angeles Prostate Cancer Index (UCLA-PCI) was the first, and is the most often used, disease-specific quality of life measurement to evaluate treatments for prostate cancer.[7]

To our knowledge, published work regarding the impact of ADT on HRQOL is scarce. The primary objective of this study was to examine the effects of ADT on the HRQOL in men with prostate cancer using the SF-36 and UCLA-PCI.

Methods

Patients and treatment

Between March 2001 and August 2004, 289 patients who underwent prostate biopsies in Chiba University Hospital were asked to fill out questionnaires addressing generic (SF-36) and disease-specific (UCLA-PCI) HRQOL before their prostate biopsy, as previously reported.[8] At this point in time, it was not known whether cancer was present or not in any patient. Needless to say, all patients were not informed of their diagnosis. Informed consent was obtained from all respondents. Among them, 123 patients were histologically proved to have prostate cancer. Consequently, they were informed of having prostate cancer and made their treatment choice (summarized in Table 1). Fifty-six men who were histologically diagnosed with prostate cancer and had received immediate ADT further participated in this prospective study. Patients were then asked to complete the same self-assessment questionnaires 3, 6 and 12 months after the start of treatment. These surveys were administered using a self-reported questionnaire to exclude observer bias. Only patients who had completed at least two HRQOL questionnaires were included in this

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Table 1 Characteristics of patients who participated in the quality of life survey at Chiba University Hospital

Treatment	PSA values (ng/mL)	Age at diagnosis (years)	Stage B ($n = 77$)	Stage C ($n = 28$)	Stage D ($n = 18$)	Total ($n = 123$)
Benign prostatic disease	9.9 ± 8.0	68.2 ± 7.7	–	–	–	166
Prostate cancer	229 ± 909	71.4 ± 7.2	77	28	18	123
Treatment						
Androgen deprivation therapy	482 ± 1309	76.0 ± 6.7	22	17	17	56†
Prostatectomy	13.0 ± 9.6	66.0 ± 4.8	36	3	0	39
External beam radiotherapy	41.9 ± 40.7	71.6 ± 4.8	8	4	1	13
Carbon ion therapy	14.1 ± 8.9	70.0 ± 3.8	3	4	0	7
Watchful waiting	10.4 ± 8.9	66.9 ± 4.6	8	0	0	8

†These patients were enrolled in this study. PSA, prostate specific antigen.

analysis. To improve compliance with completion of the HRQOL questionnaires, the goals of the study were explained to all patients.

Assessment of outcome

Health-related quality of life was assessed using the SF-36 and the UCLA-PCI.[7-9] We used the Japanese version of the SF-36 (version 1.2), which has been translated from its original English into Japanese. The validity and reliability of this version have been tested by Fukuhara and Koshinski in Japanese people chosen randomly from different generations.[10] The questionnaire includes eight scales assessing 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). Each question is scored 0–100, with higher scores indicative of a better outcome.

We also used the Japanese version of the UCLA-PCI (version 1.2), a disease-specific instrument focusing on health concerns of men treated for prostate cancer. This questionnaire has been translated into Japanese and its validity and reliability have been tested by Kakehi *et al.* [11] It includes six scales assessing urinary function, urinary bother, bowel function, bowel bother, sexual function and sexual bother. All scales are scored on a scale of 0–100, where 0 represents the worst functioning and 100 represents the best functioning.

Clinical parameters

Pretreatment blood samples were taken in the morning. Serum testosterone level was measured by radioimmunoassay using the DPC total testosterone kit (Nippon DPC, Tokyo, Japan). Serum PSA values were determined using the Architect PSA kit (Abbott, Chicago, IL, USA). Prostate volume was determined by the formula for a prostate ellipsoid (width × length × height × 0.523), using transrectal ultrasonography of the prostate. The prostate was scanned in the transverse and sagittal planes with the patient in the lithotomy position.

Statistical analyses

Quality of life scores for the various domains are shown as mean ± SE in 0–100 scales, with a higher score representing better HRQOL. The analysis focused on comparing each post-treatment HRQOL score with the pretreatment HRQOL score. A Wilcoxon signed-rank test was used to study HRQOL over time. Differences in distribution of background variables were evaluated by parametric procedures (Student's *t*-test). The inspection value was shown using the mean ± SE and the statistical analysis showed the *P*-value. Statistical significance was considered at $P < 0.05$.

Results

Patient characteristics

A total of 56 men who were histologically diagnosed with prostate cancer and who received immediate ADT participated in this study. Questionnaire responses were obtained from 40 (71.4%), 43 (76.8%) and 37 (66.1%) of 56 patients at 3, 6 and 12 months, respectively. Patients' characteristics at presentation are shown in Table 2. Mean age at diagnosis was 76.0 ± 6.7 years and the overall pretreatment serum total testosterone level was 3.90 ± 1.36 ng/mL. Clinical classification was determined in accordance with the Jewett staging system.[12] Clinical stages were as follows: stage B (T1/2N0M0), 22 patients; stage C (T3–4N0M0), 17 patients; and stage D (T1-4N1 or M1), 17 patients. There were 32 men who received maximum androgen blockade (MAB) and 24 men who received a luteinizing hormone releasing hormone (LHRH) analog or surgical castration monotherapy.

Mean PSA levels and age were significantly different among patients with different stages of cancer. In terms of PSA, values were significantly higher in patients with stage D disease compared with patients with stage B disease ($P < 0.005$) and stage C disease ($P < 0.05$). In addition, patients with stage C disease had significantly higher PSA levels than patients with stage B disease ($P < 0.005$). In terms of age, patients with stage D disease were on average 5.4 years ($P < 0.05$) younger than patients with stage B disease. Prostate cancer did not progress in any patients in the year after treatment was started, including 17 patients with stage D disease. Serum testosterone levels and prostate volume were not significantly different among groups.

36-item Short-Form Health Survey

Figure 1 presents results for SF-36 scores before prostate biopsy and at 3, 6 and 12 months after start of treatment. Men receiving ADT had few changes in SF-36 total scores or in any of the eight domains in the year after treatment, and none of the changes was statistically significant.

Subgroup analysis according to cancer stage showed that patients with stage B and C cancer (localized disease) had no statistically significant changes in the year after treatment in the total SF-36 score or its subdomains, except for a decline of vitality at 6 and 12 months ($P < 0.05$ for both). In contrast, patients with stage D cancer (metastatic disease) had significant improvements in bodily pain at 3 and 12 months

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Table 2 Characteristics of Japanese patients who had received immediate androgen deprivation therapy for prostate cancer

Clinical stage	Stage B ($n = 22$)	Stage C ($n = 17$)	Stage D ($n = 17$)	Total ($n = 56$)
Age at diagnosis, year.	78.0 ± 4.9	76.8 ± 6.3	72.6 ± 8.0†	76.0 ± 6.7
60–65	0	1	4	5
66–75	5	7	7	19
76–	17	9	6	32
Baseline serum PSA values (ng/mL)	16.7 ± 12.5	72.6 ± 62.8‡	1493 ± 2079‡*	482 ± 1309
>4–20	16	4	2	22
>20–100	6	7	1	14
>100	0	6	14	20
Baseline serum TST values (ng/mL)	3.59 ± 1.06	4.35 ± 1.7	3.86 ± 1.28	3.9 ± 1.36
≤3	8	4	5	17
>3	13	12	11	36
Unknown	1	1	1	3
Baseline prostate volume (mL)	30.1 ± 15.1	36.1 ± 13.8	34.1 ± 7.9	32.9 ± 13.5
≤50	18	14	8	40
>50–100	1	1	0	2
Unknown	3	2	9	14
Gleason's score (biopsy)				
2–6	10	1	0	11
7	9	12	3	24
8–10	2	3	14	19
Unknown	1	1	0	2
Treatment				
Androgen deprivation monotherapy	12	7	5	24
Maximum androgen blockade	10	10	12	32

†$P < 0.05$ vs stage B patients; ‡$P < 0.005$ vs stage B patients; *$P < 0.05$ vs stage C patients. PSA, prostate specific antigen; TST, testosterone.

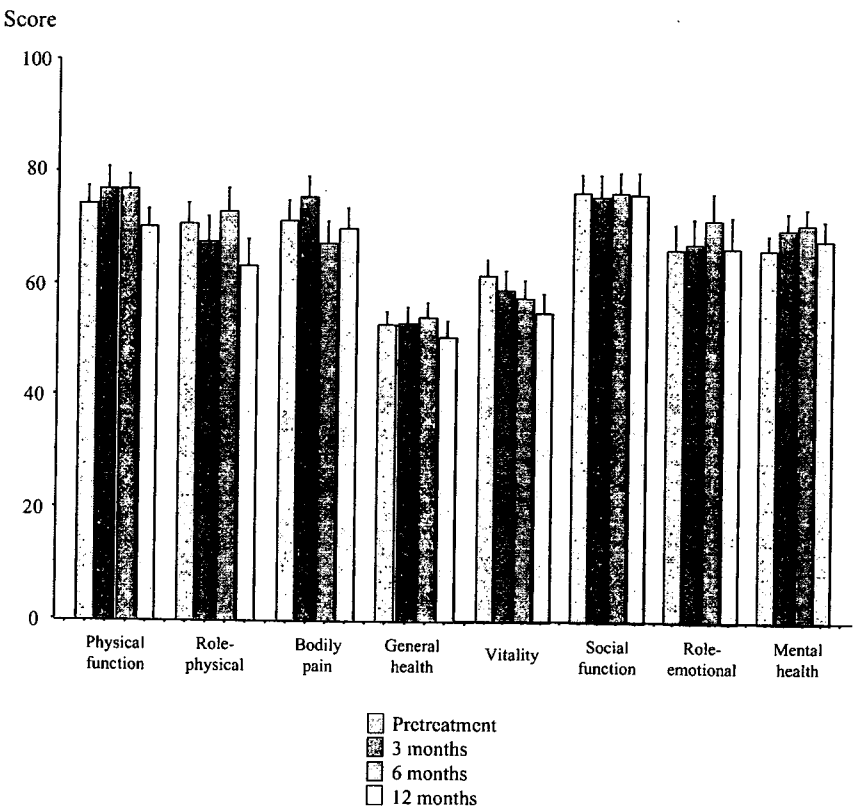

Fig. 1 The 36-item Short-Form Health Survey (SF-36) scores of Japanese patients who had received immediate androgen deprivation therapy for prostate cancer. Each domain is scored 0–100 with higher scores representing better quality of life. No statistically significant differences were observed.

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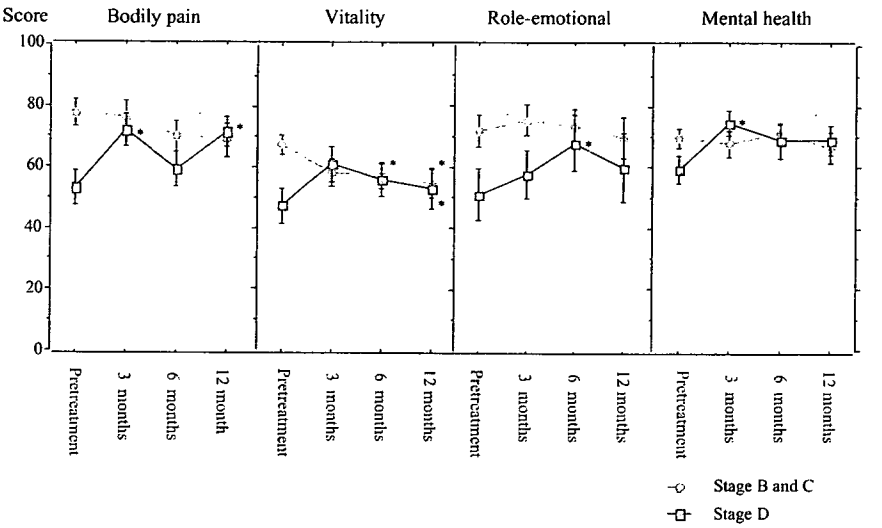

Fig. 2 Comparison of mean SF-36 scores for bodily pain, vitality, role-emotional and mental health between men with localized disease (stage B and C; ○) and metastatic disease (stage D; ■). *Statistically significant differences ($P < 0.05$).

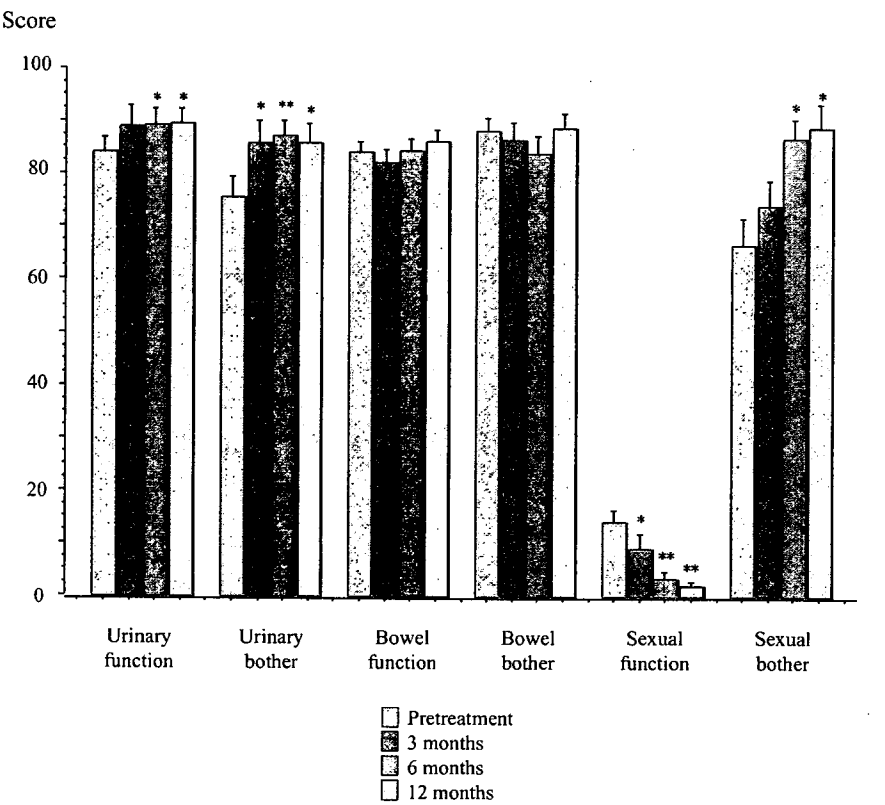

Fig. 3 University of California Los Angeles Prostate Cancer Index (UCLA-PCI) scores of Japanese patients who received immediate androgen deprivation therapy for prostate cancer. Each domain is scored 0–100 with higher scores representing better quality of life. *Statistically significant differences ($P < 0.05$). **Statistically significant differences ($P < 0.005$).

($P < 0.05$ for both), vitality at 12 months ($P < 0.05$), role-emotional at 6 months ($P < 0.05$) and mental health at 3 months ($P < 0.05$) (Fig. 2).

University of California, Los Angeles Prostate Cancer Index

Figure 3 presents results for UCLA-PCI scores before prostate biopsy and at 3, 6 and 12 months after treatment. The impact of ADT had a marked effect on urinary function, urinary bother, sexual function and sexual bother. Urinary function scores increased significantly after 6 and 12 months ($P < 0.05$ for both). In addition, urinary bother scores improved at 3 ($P < 0.05$), 6 ($P < 0.005$) and 12 months ($P < 0.05$). No significant difference was observed in bowel function or bowel bother scores at any time. Sexual function deteriorated significantly at 3 ($P < 0.05$), 6 ($P < 0.005$) and 12 months ($P < 0.005$) but, in contrast, sexual bother scores increased significantly at 6 and 12 months ($P < 0.05$ for both).

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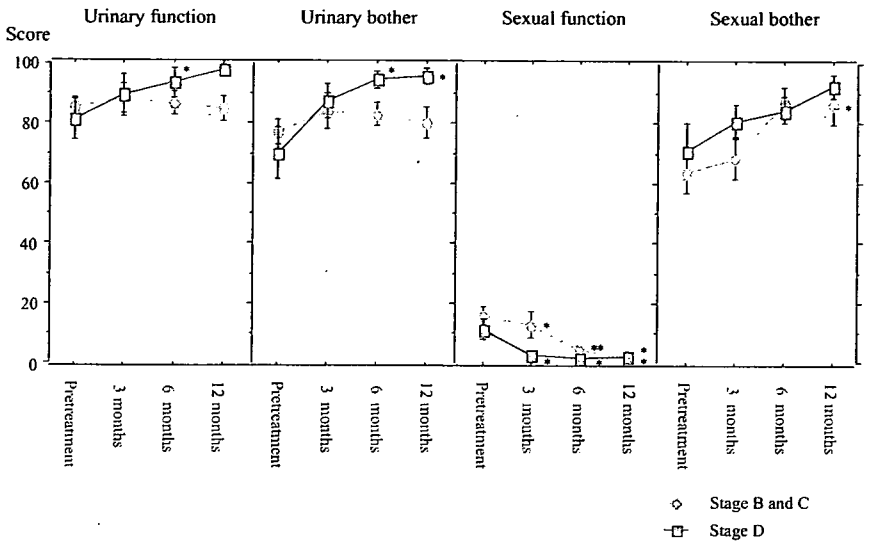

Fig. 4 Comparison of the mean UCLA-PCI scores for urinary function, urinary bother, sexual function and sexual bother in men with localized disease (stage B and C; ○) and metastatic disease (stage D; ■). *Statistically significant differences ($P < 0.05$). **Statistically significant differences ($P < 0.005$).

Subgroup analysis was done according to cancer stage. With regard to sexual domains, the similar tendency was observed, that is, marked deterioration of sexual function and increased sexual bother scores. In terms of urinary domains, patients with stage B and C disease showed no change in urinary function or bother, whereas patients with stage D disease showed a significant increase in urinary function scores at6 months ($P < 0.05$) and urinary bother scores at 6 and 12 months ($P < 0.05$ for both) (Fig. 4).

Pretreatment serum testosterone levels

A group comparison according to pretreatment serum testosterone levels was performed in SF-36 and UCLA-PCI scores between the patients with lower serum testosterone levels (=3.0 ng/mL) and those with higher testosterone levels (≤3.0). At baseline, there were no significant differences. We also longitudinally investigated the changes in the HRQOL scores according to pretreatment serum testosterone levels, however, no significant differences were seen (data not shown).

Discussion

General HRQOL

A few articles reporting the effects of hormonal treatment on HRQOL conclude that hormone therapy may significantly impair physical and emotional health of patients.[13-15] Herr and O'Sullivan reported on quality of life of asymptomatic men with non-metastatic prostate cancer on ADT.[14] They observed that ADT resulted in increased fatigue, decreased physical activity, greater emotional distress and poorer general health after 6 months and at 1 year.[14] Potosky *et al.* studied HRQOL in patients with localized prostate cancer treated initially with ADT or no therapy and reported that protracted ADT was associated with worse physical function and more fatigue compared with patients receiving no therapy.[16] Stone *et al.* reported that, in comparison with baseline assessment, fatigue increased significantly after 3 months of MAB treatment.[14] They also reported that MAB was associated with a reduction in voluntary muscle function, loss of muscle bulk, and a decline in virility and potency.

Similar to previous reports, we observed a decline of vitality in patients with stage B and C disease at 6 and 12 months. In contrast, we observed an increase of vitality in patients with stage D disease, presumably due to a decrease in bodily pain as a result of treatment.

In contrast to other studies, patients in this study, who were all Japanese, did not demonstrate impaired physical function. This result may be partially due to Japanese patients, along with other Asian groups, having low physical function at baseline and feeling less impaired. Asians are shorter, lighter and weaker than other races even after correcting for the effects of height, weight and age.[17]

Litwin *et al.* studied HRQOL in men with metastatic prostate cancer who were treated with either MAB or bilateral orchiectomy.[18] Patients receiving MAB reported significant improvements from baseline to month 12 in physical function, social function, bodily pain, emotional well-being, energy, general health perceptions, role function-physical, role function-emotional, bowel function and bowel bother.[18] Our study demonstrates that, similarly to their study, stage D patients had significant improvements in bodily pain, vitality, mental health and role-emotional.

Disease-specific HRQOL

In terms of disease-specific HRQOL, there was a substantial increase in urinary function. As expected, urinary function scores increased substantially after ADT and urinary bother scores improved, especially in patients with stage D (advanced) disease.

The deterioration of sexual function was marked throughout the treatment course. Despite a substantial decrease in sexual function, patients mostly did not experience sexual bother. Interestingly, sexual bother scores increased significantly after ADT. These results are in contrast to a previous study that showed that decreasing sexual function and increasing bother with poor sexual function were observed in a primarily European–American cohort.[19] The reason patients had high sexual bother scores, even though they had reduced function, might partly be explained by their learning how to manage their disease over time. Cultural or ethnic differences related to prostate cancer treatment appear to be important. Kakehi *et al.* stated that Japanese patients with decreased sexual activity felt less sexual bother than American patients.[11]

Namiki *et al.* performed a cross-sectional analysis of HRQOL in Japanese patients with prostate cancer who underwent prostatectomy and reported a postoperative decrease in sexual function.[20] Japanese

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patients who underwent prostatectomy were bothered by the decreased sexual activity, and not only younger (≤65 year) but also older (>65 year) patients demonstrated a decrease in sexual bother scores.[20] In contrast, our patients mostly did not experience sexual bother. The effect on HRQOL differs according to treatment choice. Patients receiving ADT felt less bothered by sexual dysfunction presumably because they are well informed of the potential for deterioration of sexual function before treatment and thus have low expectations about post-treatment sexual function. In contrast, patients undergoing prostatectomy are informed of the possibility of maintaining sexual function and thus have expectations that sexual function will be preserved.

Despite various decreases in sexual function scores, the SF-36 scores showed that general quality of life was unaffected by ADT. Confronted with similar results, Krahn *et al.* concluded that although sexual, urinary and bowel dysfunctions are common and important, their impact on the health status of prostate cancer patients may be overstated.[21]

Limitations

Our study has several limitations. First, patients participating in the study were all Japanese and thus results may not be generalizable to patients of other ethnicities. HRQOL is affected by ethnical or cultural differences, and these differences must be considered when treatment is being selected. Second, patients in this study were older, and it is not known whether these results would be applicable to younger patients. Third, patients who chose not to participate may have had HRQOL outcomes that were either better or worse than those presented in this study. Finally, UCLA-PCI is designed to evaluate treatments for early-stage prostate cancer, not advanced prostate cancer, and its query is somewhat limited. More valid and robust tool such as the Expanded Prostate Cancer Index Composite (EPIC) is needed for a comprehensive assessment. EPIC was designed to include items to assess irritative, obstructive symptoms and hormonal symptoms to compare HRQOL among various therapies.[22] Recently, the original EPIC was translated into a preliminary Japanese version and adapted to the Japanese culture, and the official version is now available.[23]

Despite these limitations, we believe that the results of this study contribute to a better understanding of the impact of ADT on HRQOL in prostate cancer patients and could provide useful information about patient-centered outcome evaluations.

We investigated HRQOL after ADT in Japanese men. General HRQOL was mostly unaffected by ADT. The deterioration of sexual function was marked throughout the treatment course. Despite a substantial decrease in sexual function, patients mostly did not suffer from sexual bother. The data reported here shed new light on the impact of ADT on quality of life in men with prostate cancer and the potential for cultural or ethnic differences in quality of life. Physicians should be aware of the possibility of ethnic or cultural differences related to HRQOL and the treatment of prostate cancer.

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Postoperative Inguinal Hernia After Radical Prostatectomy for Prostate Cancer

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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).

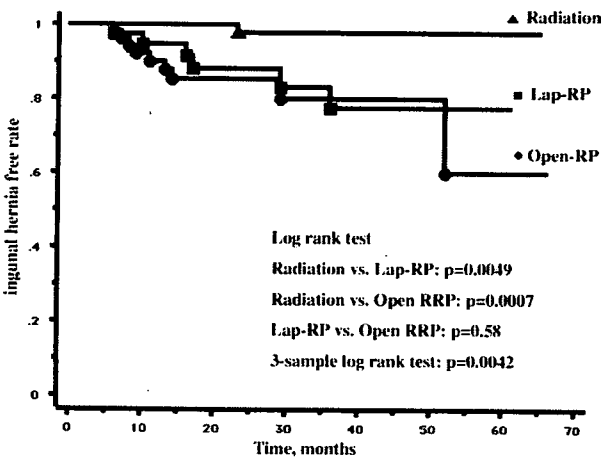

Figure 1. Kaplan-Meier plot comparing cumulative hernia-free survival in open RRP, LRP (Lap-RP), and radiotherapy groups.

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 interval; 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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Clinical Implications of Tumor Size and Local Extent of Primary Prostatic Lesions in Prostate Cancer Patients with Metastases: Value of Endorectal Magnetic Resonance Imaging in Patients with Metastases

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OBJECTIVES To investigate the clinical significance of local assessment by endorectal magnetic resonance imaging (MRI) in prostate cancer patients with metastases.

METHODS The local extent and tumor size were determined by endorectal MRI in 95 prostate cancer patients with metastases, and their clinical implications were assessed.

RESULTS The maximum diameter and tumor volume significantly correlated with the local extent of disease but not with extent of disease (EOD) on bone scan. In univariate analyses, EOD, serum prostate-specific antigen level, serum alkaline phosphatase level, and hemoglobin level were significantly associated with disease-specific survival, whereas tumor size and local extent of primary lesions were not. In a multivariate analysis EOD on bone scan was a significant prognostic factor.

CONCLUSIONS Tumor size and local extent of the primary lesion estimated by endorectal MRI were not associated with disease-specific survival. Assessment of the primary lesion by endorectal MRI is of limited value in predicting the prognosis of prostate cancer patients with metastases. UROLOGY 70: 86–90, 2007.
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Accurate pretreatment staging with identification of extracapsular extension, seminal vesicle invasion, and distant tumor spread is necessary for treatment planning in patients with prostate cancer. An estimate of prognostic factors is also considered important, and there is consequently a definitive need to evaluate the potential role of imaging methods in the prediction of individual prostate cancer biology.[1] Staging accuracy has been substantially improved thanks to the development of endorectal surface coils.[2] Furthermore, magnetic resonance imaging (MRI) with an integrated endorectal-pelvic phased-array multicoil is reported to be a useful noninvasive method for local staging of prostate cancer.[3,4] It has also been reported that endorectal MRI is useful for assessing the size of large cancer foci, as well as local extension.[5] It has been found that individual tumor volume and local extent of disease are predictors of tumor recurrence after radical prostatectomy for localized disease.[6–9] Therefore noninvasive assessment of tumor size and local extent of disease is desirable because tumor size correlates with pathologic staging, biologic aggressiveness, and tumor progression,[1] especially in patients with localized prostate cancer. To our knowledge, however, to date no study has investigated the clinical implications of tumor size and local extent of primary prostate cancer lesions assessed by endorectal MRI in prostate cancer patients with metastases. The present study was undertaken to investigate the clinical value of local assessment by endorectal MRI in prostate cancer patients with metastases.

MATERIAL AND METHODS

Ninety-five prostate cancer patients with metastases evaluated by endorectal MRI with a pelvic phased-array coil before treatment and given endocrine therapy were included in this retrospective study. The diagnosis of prostate cancer was histologically confirmed by transrectal ultrasound-guided systematic biopsy of the prostate in every patient. Nine patients had well-differentiated adenocarcinomas, 57 had moderately differentiated adenocarcinomas, and 29 had poorly differentiated adenocarcinomas. The serum levels of prostate-specific antigen (PSA) were assayed by enzyme immunoassay (E-Test Tosoh II PA; Tosoh, Tokyo, Japan).

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Table 1. Local extension and parameters

Parameter	T2	ECE	SVI	BI	RI	*P* Value
T volume (mL)	6.98 ± 2.34	15.05 ± 2.02	24.45 ± 2.46	44.55 ± 6.49	57.37 ± 12.78	<0.05
Max T diameter (cm)	2.31 ± 0.34	3.53 ± 0.18	4.02 ± 0.15	4.87 ± 0.22	5.46 ± 0.59	<0.05
PSA (ng/mL)	34.8 ± 14.2	989.3 ± 545.5	584.0 ± 254.8	910.8 ± 368.9	1131.8 ± 708	0.6129
ALP (IU/L)	268.7 ± 43.3	400.1 ± 67.0	505.0 ± 127.3	654.9 ± 217.4	399.9 ± 85.2	0.6364
Hgb (g/dL)	13.06 ± 0.4	13.55 ± 0.38	13.85 ± 0.28	13.15 ± 0.52	12.66 ± 0.39	0.3414
Histology (differentiation)						
Well	4	2	3	0	0	
Moderate	4	13	26	10	4	
Poor	2	7	12	5	3	0.0877
EOD						
0	4	6	16	6	1	
1	3	9	14	2	3	
2	2	2	7	2	1	
≥3	1	5	4	5	2	0.6603

ECE = extracapsular extension; SVI = seminal vesicle invasion; BI = bladder invasion; RI = rectal invasion; T = tumor; Max = maximum; PSA = prostate specific antigen; ALP = alkaline phosphatase; Hgb = hemoglobin; EOD = extent of disease on bone scan.

Serum alkaline phosphatase (ALP) was measured using 4-nitrophenyl-phosphate as the substrate. Serum PSA levels ranged from 6.5 ng/mL to 11,100 ng/mL (mean ± standard error, 712.0 ± 194.0 ng/mL).

The staging procedures included clinical examination, bone scan, computed tomography, and endorectal MRI. Bone metastases were detected by bone scintigraphy after intravenous injection of 25 mCi Tc-99m methylene diphosphonate. The staging evaluation revealed Stage D1 in 33 patients and Stage D2 in 62. Bone lesions were graded on the basis of the number of metastatic deposits identified on bone scans, according to the extent of disease (EOD) grading system devised by Soloway *et al.*[10] The grades were as follows: EOD 0, normal or abnormal due to benign bone disease; EOD 1, fewer than 6 metastatic sites; EOD 2, 6 to 20 metastatic sites; EOD 3, more than 20 lesions but not a superscan; and EOD 4, superscan. Thirty-nine patients were initially treated with endocrine monotherapy, including castration (medical castration using a luteinizing hormone-releasing hormone analogue or surgical castration) or estrogens. Fifty-six patients were initially treated with a combination of castration and antiandrogens. The follow-up period was 47.5 ± 3.1 months (range, 5.6 to 137.1 months).

The interval between biopsy and MRI was 33 ± 1 days. Magnetic resonance imaging was performed with a 1.5-T superconducting scanner (Signa Horizon LX, version 8.3, GE Medical Systems). The endorectal coil was inserted, and the patient was placed in the supine position between the phased-array coils. Axial T1-weighted spin echo images (time to repetition/time to echo [TR/TE] = 380 milliseconds/9 milliseconds), axial, sagittal, and coronal T2-weighted fast spin echo images (TR/TE = 3500 milliseconds/102 milliseconds, 16-echo train length), and axial T1-weighted spin echo images after injection of 0.1 mmol/kg of gadopentetate dimeglumine were obtained. The slice thickness and interslice gap were 4 mm and 0.5 mm, respectively. The criteria for diagnosis of cancer in the peripheral zone of the prostate included a low signal intensity on T2-weighted images and a homogeneously enhanced lesion lacking radiating ducts on T1-weighted images obtained after the administration of gadopentetate dimeglumine. In the central region, a ground-glass-like, homogeneous, low-signal-intensity area on T2-weighted images was another criterion. The criteria for extracapsular extension on MRI included disruption of the prostatic capsule, infiltration of the periprostatic fat, darkening of the periprostatic veins, and involvement of a neurovascular bundle.[11] Seminal vesicle invasion was detected as focal wall thickening or a low-signal-intensity area within the seminal vesicles.[11] In addition to local extent, maximal tumor diameters in three axes (width [D1], height [D2], and length [D3]) were retrospectively determined by measuring the distance directly on endorectal MR images with calipers. The estimated tumor volume was deduced using the formula for an ellipsoid object (V = 0.52 × D1 × D2 × D3).

Results are presented as the mean ± standard error. The independence of fit of categoric data was analyzed by chi-square test. Variables of different groups were compared using analysis of variance. The Spearman rank correlation test was used to evaluate the correlation between variables. The prognostic significance of tumor size, tumor histology, serum PSA level, serum ALP level, hemoglobin level, EOD grade, and endorectal MRI findings was assessed. Univariate and multivariate analyses were performed by Cox's proportional hazard model. As reported previously,[12] continuous pretreatment clinical measurements (eg, estimated tumor size) were analyzed as dichotomous variables according to approximately "optimal" cut points as follows. The value best discriminating between good and poor survival (ie, which had the most significant *P* value on a log-rank test) was found by testing all possible cut points. All such cut points were then rounded to clinically relevant (ie, convenient) values. To obtain a multivariate Cox proportional hazard model with maximum precision of the important variables, a stepwise selection procedure was used. In all analyses, $P < 0.05$ was considered statistically significant.

RESULTS

Local evaluation by endorectal MRI demonstrated no local extraprostatic extension (T2) in 10, extracapsular extension in 22, seminal vesicle invasion in 41, bladder invasion in 15, and rectal invasion in 7 patients. The maximum diameter and tumor volume significantly correlated with the local extent of disease (Table 1), whereas serum levels of PSA and ALP, histologic differ-

Table 2. Tumor histology (differentiation) and parameters

Parameter	Well	Moderate	Poor	*P* Value
T volume (mL)	8.93 ± 2.32	27.53 ± 2.89	28.40 ± 4.50	0.0501
Max T diameter (cm)	2.86 ± 0.26	4.03 ± 0.16	4.18 ± 0.24	<0.05
PSA (ng/mL)	128.5 ± 94.3	696.8 ± 175.5	923.0 ± 495.1	0.512
ALP (IU/L)	314.9 ± 95.9	572.4 ± 107.2	322.6 ± 42.5	0.186
Hgb (g/dL)	13.19 ± 0.59	13.60 ± 0.25	13.41 ± 0.29	0.7692

T = tumor; Max = maximum; PSA = prostate-specific antigen; ALP = alkaline phosphatase; Hgb = hemoglobin.

Table 3. Extent of disease on bone scan and parameters

Parameter	EOD 0	EOD 1	EOD 2	EOD ≥3	*P* Value
T volume (mL)	25.63 ± 3.81	28.74 ± 4.49	18.61 ± 3.69	27.99 ± 5.68	0.5454
Max T diameter (cm)	3.86 ± 0.24	4.16 ± 0.23	3.66 ± 0.26	4.05 ± 0.28	0.5955
PSA (ng/mL)	100.3 ± 30.4	262.5 ± 165.7	626.0 ± 177.6	2790.1 ± 809.1	<0.05
ALP (IU/L)	235.4 ± 14.6	276.4 ± 21.9	910.1 ± 334.9	925.8 ± 191.0	<0.05
Hgb (g/dL)	14.12 ± 0.20	13.85 ± 0.29	12.63 ± 0.54	12.37 ± 0.49	<0.05

EOD = extent of disease on bone scan; T = tumor; Max = maximum; PSA = prostate-specific antigen; ALP = alkaline phosphatase; Hgb = hemoglobin.

Table 4. Univariate and multivariate analysis for survival

Parameter	Univariate (*P* Value)	Multivariate		
		Hazard Ratio	95% CI	*P* Value
T volume (>25 mL)	0.1242			
Max T diameter (>3 cm)	0.3408			
Local stage (≥T3)	0.2096			
Histology (moderate and poor differentiation)	0.0852			
EOD (≥2)	0.0004	3.185	1.675–6.024	0.0004
PSA (>100 ng/mL)	0.0022			
ALP (>620 IU/L)	0.0470			
Hgb (≤12.5 g/dL)	0.0086			

CI = confidence interval; T = tumor; Max = maximum; PSA = prostate-specific antigen; ALP = alkaline phosphatase; Hgb = hemoglobin.

entiation, and EOD on bone scan did not (Table 1). The tumor volume in well-differentiated adenocarcinoma was 8.93 ± 2.32 mL, which was significantly (P <0.05) smaller than that of moderately and poorly differentiated adenocarcinoma (27.82 ± 2.43 mL). The maximum tumor diameter significantly (P <0.05) correlated with tumor histology, but serum levels of PSA and ALP and hemoglobin levels did not (Table 2).

On the other hand, tumor volume and maximum tumor diameter did not significantly correlate with EOD (Table 3), but serum levels of PSA and ALP significantly increased and hemoglobin levels significantly decreased with higher EOD grade (Table 3). Tumor volume and maximum tumor diameter significantly correlated with serum PSA levels (P <0.05 and P <0.05, respectively) but not with serum ALP levels (P = 0.4406 and P = 0.3033, respectively) and hemoglobin levels (P = 0.367 and P = 0.9877, respectively). In univariate analyses, EOD on bone scan, serum PSA level, serum ALP level, and hemoglobin level were significantly associated with disease-specific survival, whereas tumor volume, maximum tumor diameter, and local extent of primary lesions were not (Table 4). In a multivariate analysis, EOD on bone scan was an independent prognostic factor for prostate cancer patients with metastases (Table 4).

COMMENT

It has been proposed that the biologic aggressiveness of prostate cancer is a direct function of tumor volume.[13] Bostwick *et al.*[14] evaluated the utility of tumor volume in predicting progression of early prostate cancer and found that tumor volume correlates with the probability of capsular invasion, seminal vesicle invasion, and metastases in clinically localized prostate cancer. Histopathologic investigations also demonstrated that organ-confined prostate tumors have a significantly lower volume than those with extraprostatic extension.[15] It has also been reported that maximum tumor diameter was associated with tumor volume, Gleason score, and pathologic stage in clinically localized prostate cancer.[9] In the present study, the local extent of primary lesions correlated with tumor size, which was associated with tumor histology even in patients with metastatic prostate cancer. It is reasonable to assume that high-grade tumors are larger in size and locally advanced. In other words, tumor size may be related to the capability for local invasion,

because a large tumor may indicate the rapid growth of a high-grade tumor.[1]

It is known that serum PSA levels significantly correlate with the local extent of disease in patients with localized prostate cancer and with EOD on bone scan in those with metastatic prostate cancer. In the present study, however, serum levels of PSA and ALP did not correlate with the local extent of disease in patients with metastases, although serum levels of PSA and ALP significantly correlated with EOD, as previously reported.[16] In addition, tumor size did not correlate with EOD, suggesting that the size of primary lesions is not a significant factor related to tumor burden due to distant metastases. Furthermore, no significant association was found between local extent of primary lesions and EOD on bone scan. These data suggest that biologic features of primary lesions, such as tumor size and local extent of disease, are not related to the metastatic burden represented by EOD and that serum PSA and ALP may reflect tumor burden due to distant metastatic lesions rather than primary lesions in patients with metastases.

A volume-based prognostic index has been proposed as an adjunct to staging for early prostate cancer.[14] It has been reported that tumor volume estimated from prostatectomy specimens correlated with the risk of failure after radical prostatectomy in localized prostate cancer.[7] Stamey *et al.*[6] have also found that tumor volume is an independent prognostic factor. On the other hand, Kikuchi *et al.*[17] have reported that in multivariate analysis tumor volume was not a significant independent predictor of prognosis, although in univariate analysis tumor volume strongly correlated with the probability of progression. They concluded that tumor volume provided no independent prognostic information when considered in multivariate analysis together with Gleason score and pathologic stage in localized prostate cancer.[17] Thus the prognostic value of tumor size is still controversial, even in localized prostate cancer. Recently Renshaw *et al.*[18] reported that in radical prostatectomy specimens tumors can be stratified by size according to simple measurements obtainable during routine pathology practice in clinically localized prostate cancer. It has been reported that the greatest tumor dimension is a simple, inexpensive predictor of PSA failure in men who have undergone radical prostatectomy.[8,9] It is known that the local extent of disease is a significant prognostic factor in localized prostate cancer. D'Amico *et al.*[19,20] have suggested that preoperative endorectal coil MRI results provide statistically independent prognostic information about postoperative PSA failure. However, the prognostic value of tumor size and local extent of disease has not been fully elucidated in patients with advanced prostate cancer. In the present study, univariate analyses showed that EOD on bone scan, serum PSA level, and serum ALP and hemoglobin levels were significantly associated with disease-specific survival, which was in agreement with the results of a previous study,[21] whereas tumor volume, maximum tumor diameter, and local extent of primary lesions estimated by endorectal MRI were not. Although the size and local extent of primary prostate cancer lesions are not evaluated by histopathologic examination, local assessment by endorectal MRI provides little information for the prognosis in patients with metastases. In multivariate analysis, EOD on bone scan was an independent prognostic factor for prostate cancer patients with metastases.

CONCLUSIONS

The size of primary lesions significantly correlated with tumor histology and local extent of disease, whereas tumor size and local extent of primary lesions estimated by endorectal MRI were not associated with EOD on bone scan nor with disease-specific survival. The assessment of primary lesions by endorectal MRI is of limited value in predicting the prognosis of prostate cancer patients with metastases.

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Persistent expression of Aurora-A after neoadjuvant hormonal therapy as a predictor of a poor clinical outcome in patients undergoing radical prostatectomy for prostate cancer

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OBJECTIVES

To characterize the changes in the expression of Aurora-A protein in prostate cancer before and after androgen-withdrawal therapy, and to assess the prognostic significance of the Aurora-A expression in patients undergoing radical prostatectomy (RP) after neoadjuvant hormonal therapy (NHT).

PATIENTS AND METHODS

The study included 97 patients with clinically localized prostate cancer who received NHT followed by RP. Paired needle biopsy and corresponding RP specimens obtained from these patients were analysed for the expression of Aurora-A protein by immunohistochemical staining. These findings were then evaluated in relation to several clinicopathological factors.

RESULTS

There were various levels of Aurora-A protein expression in most prostate cancer tissues before NHT; however, the Aurora-A expression in RP specimens after NHT was significantly down-regulated compared with that in corresponding needle-biopsy specimens. The expression level of Aurora-A in biopsy specimens was significantly associated with the biopsy Gleason score, but not with other factors available before RP. The Aurora-A expression in the RP specimens correlated significantly with the preoperative value of the serum prostate specific antigen and pathological stage, but not with any other clinicopathological factors examined. Furthermore, cell proliferative activity in the RP specimens, measured by Ki-67 immunostaining, was proportional to the expression of Aurora-A. The biochemical recurrence-free survival in patients with a persistent Aurora-A expression in RP specimens was significantly lower than that in those with a weak Aurora-A expression, but the expression level of Aurora-A was not an independent predictor of biochemical recurrence.

CONCLUSIONS

Despite the lack of any independent significance, the expression level of Aurora-A in prostate cancer tissue after NHT, which might inversely reflect the therapeutic effect of NHT, could therefore be a useful variable for predicting biochemical recurrence in patients undergoing RP.

KEYWORDS

Aurora-A, prostate cancer, neoadjuvant hormonal therapy, radical prostatectomy

INTRODUCTION

The centrosome ensures an equal segregation of chromosomes to the post-mitotic daughter cells, by organising the bipolar mitotic spindle during normal cell proliferation; however, multipolar mitotic spindles and various types of cetrosomal anomalies are frequent in cancer cells [1]. Such abnormalities might cause the disruption of normal chromosomal segregation and result in the production of aneuploid cells. Although the precise molecular mechanisms regulating segregation of chromosomes have not been well characterized, several genes involved in the function mediating centrosome duplication were recently cloned and analysed, including members of mammalian Aurora homologues [2].

Aurora-A, a serine/threonine protein kinase belonging to the *Drosophila aurora* and *Saccharomyces cerevisiae* Ip11 kinase family, has been shown to be crucial in chromosome segregation and centrosome functions [3].

Because of its location on chromosome 20q13, a region frequently amplified in various types of human malignant tumours, Aurora-A has attracted intense interest [4,5]. Indeed, there is marked up-regulation of Aurora-A in several kinds of human cancer specimens [3,6,7]. In addition, recent studies showed that introducing the *Aurora-A* gene into mouse NIH/3T3 cells and Rat 1 fibroblasts leads to transformation *in vitro* and tumorigenesis *in vivo* [8,9]. Collectively, these findings suggest that if overexpressed, Aurora-A could function as an oncogene through the abnormal regulation of centrosome function.

Also in prostate cancer, several studies have shown the important roles of centrosomal defects and chromosomal instability in disease progression [10,11]. Furthermore, recent studies reported that Aurora-A is overexpressed in high-grade prostatic intraepithelial neoplasia and primary prostate cancer lesions, and that expression patterns of Aurora-A correlate with several potential prognostic variables [12,13]. Considering these findings, it would be of interest to investigate whether Aurora-A is involved in adaptive changes in prostate cancer induced by hormonal therapy. However, to our knowledge, there have been no studies characterizing the changes in Aurora-A

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Immunostaining	N(%) Needle biopsy	RP	P
Intensity			<0.001
+1	1 (1)	24 (25)	
+2	35 (36)	31 (32)	
+3	41 (42)	37 (38)	
+4	20 (21)	5 (5)	
Extent			<0.001
+1	1 (1)	12 (12)	
+2	5 (5)	16 (17)	
+3	11 (11)	20 (21)	
+4	80 (83)	49 (51)	
Score			0.006
≤8	41 (42)	60 (62)	
≥9	56 (58)	37 (38)	

TABLE 1
Results of Aurora-A immunostaining on paired needle biopsy and RP specimens from 97 patients who had NHT

expression and its prognostic significance in prostate cancer after androgen-withdrawal therapy. Accordingly, we initially compared the expression of Aurora-A protein in paired needle biopsy and radical prostatectomy (RP) specimens from patients who had had neoadjuvant hormonal therapy (NHT) before RP, and further analysed the correlation of Aurora-A expression with several clinicopathological factors.

PATIENTS AND METHODS

This study included 97 patients who were diagnosed by transrectal needle biopsy as having prostate cancer, and subsequently received NHT using a LHRH agonist (3.6 mg goserelin acetate or 3.75 mg leuprorelin acetate every 4 weeks) plus antiandrogen (80 mg bicalutamide or 375 mg flutamide daily) followed by RP, at our institution between April 1993 and December 2004. The median (range) duration of the follow-up after RP was 47 (10–152) months. Informed consent to the study was obtained from each patient, and the study design was approved by the Research Ethics Committee of our institution. Specimens were examined pathologically by a one pathologist, according to the 2002 TNM system. After RP, patients were usually followed by measurements of serum PSA level every ≤3 months for the first 2 years and every 6 months thereafter. Biochemical recurrence was defined as a PSA level persistently >0.2 ng/mL. Irrespective of pathological findings suggesting a poor prognosis, none of the patients received any adjuvant therapy until biochemical recurrence was detected.

The prostate cancer specimens were stained immunohistochemically as previously described [14]; briefly, sections from formaldehyde-fixed, paraffin-embedded tissue from 97 specimens were deparaffinized by xylene and rehydrated in decreasing concentrations of ethanol. After blocking endogenous peroxidase with 3% hydrogen peroxidase in methanol, sections were boiled in 0.01 M citrate buffer for 10 min and incubated with 5% normal blocking serum for 20 min The sections were then incubated with antihuman Aurora-A rabbit polyclonal antibody (Abcam, Cambridge, UK) and antihuman Ki-67 mouse monoclonal antibody (Dako, Carpinteria, CA, USA) for 2 h at room temperature, followed by incubation with biotinylated goat anti-rabbit or mouse IgG (Vector Laboratories, Burlingame, CA, USA) for 30 min. After incubation in an avidin-biotin peroxidase complex for 30 min, the samples were exposed to diaminobenzidine tetrahydrochloride solution and counterstained with haematoxylin. Negative controls, in which PBS was used instead of the primary antibody, were run with each batch of staining samples, while s.c. inoculated human androgen-independent prostate PC3 tumours were used as a positive control, as previously described [13]. Staining results were interpreted by two independent observers (J.F. and A.T.) who were unaware of the clinicopathological data of the patients. For Aurora-A analysis, staining intensity was scored from +1 (no staining), +2 (weak), +3 (medium) to +4 (strong), and staining extent was also scored from +1 (0–10%), +2 (11–25%), +3 (26–50%) to +4 (51–100%). The product of staining intensity and staining extent was defined as the staining score. In addition, only nuclear staining was considered when evaluating Ki-67 staining, and strong expression of Ki-67 was defined as the proportion of positively stained tumour cells >5%.

Several clinicopathological factors of the patients were analysed using the chi-square test. The biochemical recurrence-free survival rates were calculated by the Kaplan-Meier method, and differences assessed using the log-rank test. The prognostic significance of some factors was assessed by the Cox proportional hazards regression model; in all tests $P < 0.05$ was considered to indicate significance.

RESULTS

The findings of Aurora-A immunostaining in paired needle biopsy and corresponding RP specimens from 97 patients are shown in Table 1. Although Aurora-A protein was present in the cytoplasm of prostate cancer cells in most biopsy specimens, there was no detectable Aurora-A expression in 24 RP specimens (25%). Furthermore, both staining intensity and the extent of Aurora-A expression in RP specimens after NHT were significantly lower than those in biopsy specimens. When we defined any staining score of >8 as indicating strong expression, 56 (58%) and 37 (38%) patients were regarded as having prostate cancer with strong Aurora-A expression on biopsy and RP specimens, respectively. Representative findings of immunohistochemical studies based on this system are shown in Fig. 1.

We subsequently assessed the correlation of Aurora-A staining on needle biopsy and RP specimens with several clinicopathological variables. In biopsy specimens, the expression level of Aurora-A protein was significantly associated with biopsy Gleason score, but there was no significant relation of the Aurora-A expression level to other factors available before RP, including age, serum PSA level and percentage of positive biopsy cores (Table 2). On RP specimens after NHT, Aurora-A protein expression was significantly associated with preoperative serum PSA level and pathological stage, but not other pathological factors, including Gleason score, perineural invasion and lymph node metastasis. Furthermore, cell proliferative activity in the RP specimens, measured by

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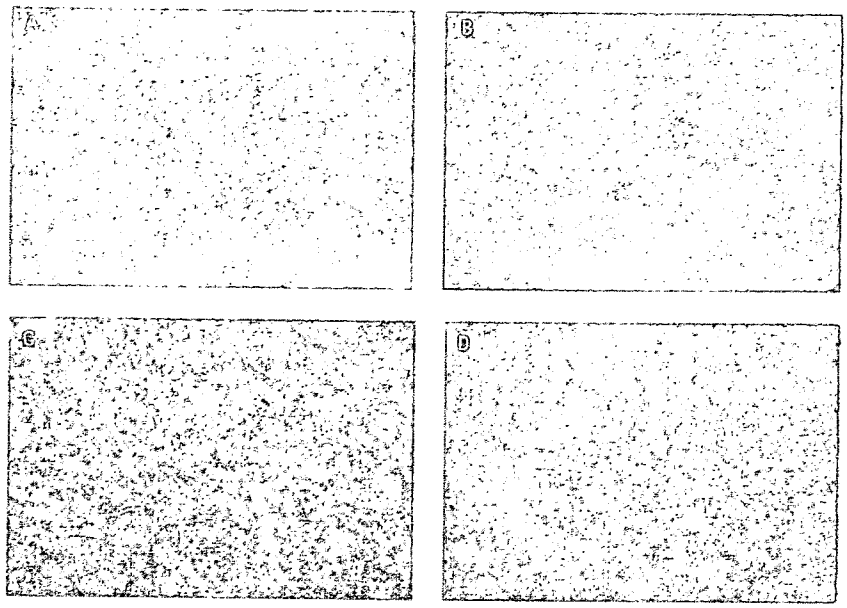
Ki-67 immunostaining, was in proportion to the expression level of Aurora-A (Table 2).

There was no significant difference in overall survival between patients with strong and weak Aurora-A expression (data not shown). During the present observation period biochemical recurrence developed in 21 of 97 patients (22%); there was biochemical recurrence occurred in 13 of the 37 (35%) with strong and in eight of 60 (13%) with weak Aurora-A expression in RP specimens. Biochemical recurrence-free survival in patients with strong Aurora-A expression was significantly lower than that in those with weak expression (Fig. 2). Furthermore, to evaluate the predictive value of several clinicopathological factors for biochemical recurrence, we used a multivariate analysis using the Cox proportional hazard regression model. As shown in Table 3, only lymph-node metastasis was independently associated with biochemical recurrence, irrespective of other factors examined.

FIG. 1. Representative findings of immunohistochemical staining of Aurora-A expression in prostate cancer. Biopsy specimens showing (A) weak, (B) strong expression; and RP specimens showing (C) weak and (D) strong expression of Aurora-A.



DISCUSSION

Although >80% of patients with prostate cancer initially respond to androgen-withdrawal therapy, progression to androgen-independence ultimately occurs within a few years in most of these patients. To date, various molecular mechanisms involved in androgen-independent progression have been reported, amongst which adaptive up-regulation of anti-apoptotic genes and/or persistent overexpression of cell survival genes, e.g. bcl-2, bcl-xL, clusterin, IGF binding protein-2 and -5 and heat-shock protein 27 (HSP27), is currently regarded as one of the most important events contributing to the acceleration of the acquisition of an androgen-independent phenotype [15]. Furthermore, our previous studies identified changes in the expression levels of these genes after NHT as useful predictors of biochemical outcome in patients undergoing RP [16,17].

Recently, Aurora-A, a key regulator of centrosome function, has attracted great interest, as several studies recently showed that overexpression of Aurora-A results in disruption of normal cell-cycle progression, and subsequently promotes oncogenic transformation [2,3,8,9]; however, the effects of NHT on changes in Aurora-A expression in prostate cancer, and its clinical significance, remain largely unknown. Hence, we evaluated the expression of Aurora-A protein by immunohistochemical staining in paired needle biopsy and corresponding RP specimens obtained from patients who had had NHT before RP.

In this series, despite the expression of Aurora-A protein in most prostate cancer tissues in needle-biopsy specimens before NHT, the markedly lower Aurora-A expression in the RP specimens than in the corresponding biopsy specimens was confirmed. However, there was persistent strong expression in ≈ 40% of RP specimens. The patterns of change in Aurora-A expression before and after androgen withdrawal do not parallel the patterns of changes in proteins with anti-apoptotic activity, e.g. clusterin and HSP27, suggesting the involvement of Aurora-A in the process of progression to androgen-independence in a manner differing from those of previously characterized anti-apoptotic genes [15–17].

There was a significant correlation of Aurora-A expression in biopsy specimens with the Gleason score, but no correlation with other variables before RP. This finding is supported by the results of Lee *et al.* [13], who identified a strong association between Aurora-A expression in human prostate cancer cell lines and its corresponding biological malignant potential. We also found that persistent overexpression of Aurora-A in RP specimens after NHT was marked in patients with a higher preoperative serum PSA and pathological stage. Cell proliferative activity in the RP specimens, measured by Ki-67 immunostaining, was also in proportion to the expression level of Aurora-A, suggesting that down-regulation of Aurora-A after NHT would reflect an indirect effect of reduced cell proliferation rather than that of androgen regulation of this gene. Considering these findings, it would be interesting to investigate the value of a novel therapeutic strategy

FIG. 2. Biochemical recurrence-free survival of patients with prostate cancer according to Aurora-A expression status in RP specimens after NHT, by Kaplan-Meier analysis.

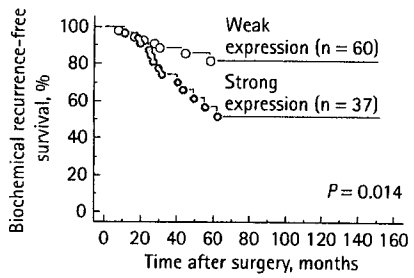


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TABLE 2 Correlation of Aurora-A expression with several factors in needle-biopsy specimens before NHT and RP specimens after NHT

Variables	No. of patients	Staining intensity +1–2	+3–4	P	Staining extent +1–2	+3–4	P	Staining score ≤8	≥9	P
Needle biopsy										
Age, years				0.770			0.850			0.400
≤69	52	20	32		3	49		24	28	
≥70	45	16	29		3	42		17	28	
Serum PSA (ng/mL)				0.620			0.390			0.960
≤9.9	12	5	7		1	11		5	7	
≥10–19.9	41	17	24		3	38		18	23	
≥20.0	44	14	30		2	42		18	26	
Biopsy Gleason score				0.030			0.001			0.029
≤6	22	12	10		5	17		14	8	
7	48	19	29		1	47		20	28	
≥8	27	5	22		0	27		7	20	
% of positive biopsy core				0.370			0.570			0.410
≤49	59	24	35		3	56		23	36	
≥50	38	12	26		3	35		18	20	
RP specimens										
Age, years				0.830			0.990			0.730
≤69	52	30	22		15	37		33	19	
≥70	45	25	20		13	32		27	18	
Preop. serum PSA (ng/mL)				0.010			0.028			0.023
≤0.09	56	38	18		21	35		40	16	
≥0.1	41	17	24		7	34		20	21	
Pathological stage				0.021			0.013			0.011
≤pT2	50	34	16		20	30		37	13	
≥pT3	47	21	26		8	39		23	24	
Gleason score				0.480			0.980			0.960
≤6	25	15	10		7	18		15	10	
7	49	29	20		14	35		31	18	
≥8	23	11	12		7	16		14	9	
Perineural invasion				0.620			0.690			0.390
Negative	42	25	17		13	29		28	14	
Positive	55	30	25		15	40		32	23	
Lymph node metastasis				0.620			0.800			0.140
pN0	89	51	38		26	63		57	32	
pN1	8	4	4		2	6		3	5	
Ki-67 expression				0.021			0.010			0.030
weak	83	51	32		28	55		55	28	
strong	14	4	10		0	14		5	9	

TABLE 3 Association of variables with biochemical recurrence-free survival in patients with prostate cancer who had RP after NHT

Variable	Hazard ratio (95% CI)	P
Age, years (≤69 vs ≥70)	1.12 (0.71–4.10)	0.520
Preop. serum PSA level, ng/mL (≤0.09 vs ≥0.1)	1.33 (0.60–3.77)	0.290
Pathological stage (≤pT2 vs ≥pT3)	1.71 (0.57–2.44)	0.110
Gleason score (≤6 vs ≥7)	1.37 (0.20–4.92)	0.610
Perineural invasion (–ve vs +ve)	1.70 (0.44–6.89)	0.420
Lymph node metastasis (pN0 vs pN1)	3.45 (1.08–8.23)	0.037
Ki-67 expression in RP (weak vs strong)	1.50 (0.37–3.44)	0.230
Aurora-A score in RP (weak vs strong)	1.55 (0.42–3.15)	0.200

targeting the *Aurora-A* gene, to further enhance the pro-apoptotic effect of NHT on prostate cancer cells.

Despite the lack of independent significance, biochemical recurrence-free survival in patients with strong Aurora-A expression in the RP specimens was significantly lower than that in those with weak expression. Although the expression level of Aurora-A protein in prostate cancer specimens from patients who were not treated by NHT has already been shown to be associated with several prognostic factors, to our knowledge, this is the first study to identify persistent expression of Aurora-A after NHT as a significant prognostic predictor. These findings indicate that persistent overexpression of Aurora-A after NHT might inversely reflect its therapeutic effect, and that persistent expression of Aurora-A after NHT could be a potential adjunct to conventional predictors of biochemical recurrence in patients undergoing RP.

The present study has some limitations; at our institution, RP is usually used with no previous NHT, resulting in a recruitment time for the 97 patients of >10 years. Such a long recruitment time could affect clinical outcomes, due to recent changes associated with the treatment of prostate cancer, e.g. progress in surgical techniques and the introduction of novel therapeutic methods for recurrent disease. In addition, there are several factors that cause biases in the present results; e.g. the evaluation of Aurora-A expression in biopsy specimens might not completely reflect that of the RP specimens in each case. It would also bias the biochemical recurrence-free survival to combine RP with NHT. Finally, the expression level of Aurora-A in RP specimens was shown to lack independent significance as a predictor of biochemical recurrence, which could be explained by the significant correlation of Aurora-A expression with potential prognostic indicators. Collectively, these findings suggest that it would be necessary to include more patients with a longer follow-up to draw definitive conclusions about the significance of Aurora-A expression level in RP specimens after NHT.

In conclusion, the expression of Aurora-A was significantly lower in RP specimens than in biopsy specimens before NHT, but persistent overexpression of Aurora-A was detected in ≈ 40% of RP specimens after NHT. Moreover,

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despite the lack of independent significance, the expression level of Aurora-A in prostate cancer tissue after NHT, which might inversely reflect the therapeutic effect of NHT, could be a useful variable predicting biochemical recurrence in patients undergoing RP.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **RP**, radical prostatectomy; **NHT**, neoadjuvant hormonal therapy; **HSP**, heat-shock protein.

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