RESULTS

Changes in the PSA levels within 1 month before prostate biopsy (pretreatment), after 6 months of endocrine treatment, 8 months of endocrine treatment (immediately after EBRT), and 14 months of endocrine treatment (6 months after EBRT) are shown in Table II. The PSA levels showed a remarkable decrease to median (mean ± SD) levels of 1.1 ng/ml (2.7 ± 5.0), 0.2 ng/ml (0.6 ± 1.0) and 0.1 ng/ml (0.3 ± 0.5) after 6, 8, and 14 months of the protocol treatment, respectively. The proportion of patients with PSA levels of 1.0 ng/ml or lower was 49% (85/173), 81% (118/145), and 91% (86/95) at 6, 8, and 14 months of the protocol treatment.

Of the 157 cases treated with EBRT, excluding eliminated cases without recurrence of disease, 153 cases (97.5%) had no biochemical failure in the mean follow-up of 17.3 months (range from 6.7 to 34.3 months).

A total of 44 cases were treated by intermittent hormonal therapy. Of the 44 cases, 41 cases have had no endocrine treatment according to the criteria after 14 months of the protocol treatment. Of the 401 months of the post-intermittent phase (i.e., after 14 months in the protocol treatment), in all 44 cases, 394 months (98.3%) were without treatment with endocrine therapy according to the criteria (off-treatment).

Of the 44 cases within the intermittent treatment protocol, 3 cases (6.8%) resumed endocrine therapy, because of clinical progression in 1 case and PSA levels increasing to greater than 10 ng/ml in 2 cases.

DISCUSSION

Although the treatment efficacy of intermittent endocrine therapy has not been clarified, it would be expected to have significance in the QOL, cost and prevention of decreasing bone mineral density. Several investigators have demonstrated the possibility of the clinical utility of intermittent endocrine therapy. The proportion of off-treatment periods were 38–50% during 24–30 months of follow-up periods in men with prostate cancer treated with endocrine monotherapy [8–10]. Most of the non-randomized trials have reported a response to the reintroduction of hormonal therapy in 90% of patients, with an on-treatment/off-treatment ratio of about 40–60% [8,11–17]. However, there had been no RCT to investigate the possibility of intermittent endocrine therapy in combination with EBRT in men with locally advanced prostate cancer. The biochemical recurrence rate may be higher in men treated with intermittent endocrine therapy than in those with continuous endocrine therapy. However, additional EBRT may improve disease-free survival for men with locally advanced prostate cancer. The present study revealed that the on-treatment/off-treatment ratio was extremely low at 1.8%. Therefore, the present RCT can solve uncertainties of treatment efficacy and QOL for intermittent endocrine therapy in combination with EBRT for men with locally advanced prostate cancer.

In the present study, disease-free survival was defined as a primary endpoint, because a previous study demonstrated a high 5-year overall survival rate of 92% and a relatively low 5-year biochemical disease-free survival rate of 61% in patients with locally advanced prostate cancer treated with LHRH agonist alone [7]. To set biochemical disease-free survival as the primary endpoint, it may be possible to have enough statistical power during a 5-year follow-up. The validity of this setting may be acceptable, because there is a limitation to the treatment after developing hormone-insensitive prostate cancer. Furthermore, any endocrine treatments will not be effective after recurrence of disease and the life span may be limited.

TABLE II. Changes in the PSA Levels After 6, 8, and 14 Months of the Protocol Treatment

	0 month	6 months	8 months	14 months
n	215	173	145	95
PSA level (ng/ml)				
Mean ± SD	45.1 ± 64.3	2.7 ± 5.0	0.6 ± 1.0	0.3 ± 0.5
Median	25.3	1.1	0.2	0.1
PSA distribution				
0.0–1.0	0 (0.0%)	85 (49.1%)	118 (81.4%)	86 (90.5%)
1.1–2.0	0 (0.0%)	29 (16.8%)	14 (9.7%)	9 (9.5%)
2.1–4.0	3 (1.4%)	33 (19.1%)	11 (7.6%)	0 (0.0%)
4.1–10.0	38 (17.7%)	15 (8.7%)	2 (1.4%)	0 (0.0%)
10.1–20.0	41 (19.1%)	6 (3.5%)	0 (0.0%)	0 (0.0%)
20.1–50.0	79 (36.7%)	5 (2.9%)	0 (0.0%)	0 (0.0%)
50.1–100.0	33 (15.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
100.1–∞	21 (9.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

The rates of biochemical no evidence of disease (bNED) control for patients with stage T3/T4 disease treated with a conventional dose of radiation therapy alone are poor, between 25 and 32% at 5 years [18,19] and 37% at 6 years [20]. The 5-year bNED in patients treated with EBRT alone for stage T1 to T4 disease decreased as pretreatment PSA levels increased, that is a bNED of 82–100%, 44–66%, 27–72%, and 11–14% for patients with pretreatment PSA levels of 4 ng/ml or less, 4–10 ng/ml, 10–20 ng/ml, and greater than 20 ng/ml, respectively [18,20–22]. The bNED control rate is higher in men treated with 3DCRT than in those treated with conventional EBRT even for cases with high levels of PSA. However, the bNED at 5 years is still low at 75 and 32% in patients treated with a high radiation dose of 76 Gy, in the PSA range of 10–20 ng/ml and greater than 20 ng/ml, respectively [23]. These treatment failures might result from the limitation of EBRT for large volume cancer on one side and the existence of clinically undetectable metastasis on the other side.

These poor outcomes of EBRT for locally advanced prostate cancer led to several randomized controlled trials on the effectiveness of neoadjuvant or adjuvant hormonal therapy in comparison with EBRT alone by the Radiation Therapy Oncology Group (RTOG) and The European Organization for Research and Treatment of Cancer (EORTC).

The RTOG 86-10 was conducted to investigate the usefulness of androgen ablation 2 months before and during EBRT compared with EBRT alone for locally advanced prostate cancer [5]. The biochemical disease-free survival and cause-specific mortality were significantly better in men undergoing androgen ablation before and during EBRT than in those treated with EBRT alone, especially in patients with Gleason 2–6 tumors.

Bolla et al. [3] conducted an RCT comparing overall survival and the disease-free interval between men treated with EBRT alone and with EBRT in combination with 3 years of adjuvant endocrine therapy starting from the initial date of EBRT (EORTC 22863) [3]. They demonstrated that the 5-year overall survival rate was significantly higher at 79% in patients treated with combination therapy than that in those treated with EBRT alone, which was 62%. The 5-year disease-free survival rate was also significantly higher at 81% in patients treated with combination therapy than that in those treated with EBRT alone.

The effectiveness of adjuvant endocrine therapy in combination with EBRT for patients with locally advanced prostate cancer can be clarified. Although cancer volume may be a very important factor in the treatment of EBRT, clinical data addressing the potential value of hormonal cytoreduction before radiotherapy have been quite limited. Therefore, it can also be valuable to investigate whether neoadjuvant endocrine therapy before EBRT is useful for locally advanced prostate cancer. In the present study protocol, all patients were initially treated with endocrine therapy for 6 months, and only patients with PSA levels after 6 months of endocrine therapy of 10 ng/ml or lower and also lower than the pretreatment levels were enrolled as final candidates in this study. The eliminated cases without sufficient effects after 6 months of endocrine treatment should be treated with other treatment protocols like chemoendocrine treatment. Therefore, our study protocol, which selects only patients with sufficient effects by neoadjuvant endocrine treatment, may be acceptable by means of ethical issues and also scientific validity.

At present, EBRT in combination with adjuvant endocrine therapy for locally advanced prostate cancer can be recommended in terms of survival benefit. However, it has not been clarified when and how long additional endocrine therapy should be conducted with respect to not only survival but also QOL. The compliance of this RCT may be high, so it is expected that long-term follow-up of the participants in the present study will reveal the possibilities of intermittent endocrine therapy after EBRT in patients with locally advanced prostate cancer.

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Featured Article

The Influence of Androgen Deprivation Therapy on Dihydrotestosterone Levels in the Prostatic Tissue of Patients with Prostate Cancer

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ABSTRACT

Purpose: **The influence of androgen deprivation therapy on dihydrotestosterone levels in the prostatic tissue is not clearly known. Changes in dihydrotestosterone levels in the prostatic tissue during androgen deprivation therapy in the same patients have not been reported. We analyzed dihydrotestosterone levels in prostatic tissue before and after androgen deprivation therapy.**

Experimental Design: **A total of 103 patients who were suspected of having prostate cancer underwent prostatic biopsy. Sixty-nine patients were diagnosed as having prostate cancer whereas the remaining 34 were negative. Serum samples were collected before biopsy or prostatectomy. Dihydrotestosterone levels in prostatic tissue and serum were analyzed using liquid chromatography/electrospray ionization-mass spectrometry after polar derivatization. In 30 of the patients with prostate cancer, dihydrotestosterone levels in prostatic tissue were determined by performing rebiopsy or with prostate tissues excised after 6 months on androgen deprivation therapy with castration and flutamide.**

Results: **Dihydrotestosterone levels in prostate tissue after androgen deprivation therapy remained at ~25% of the amount measured before androgen deprivation therapy. Dihydrotestosterone levels in serum decreased to ~7.5% after androgen deprivation therapy. The level of dihydrotestosterone in prostatic tissue before androgen deprivation therapy was not correlated with the serum level of testosterone. Serum levels of adrenal androgens were reduced to ~60% after androgen deprivation therapy.**

Conclusions: **The source of dihydrotestosterone in prostatic tissue after androgen deprivation therapy involves intracrine production within the prostate, converting adrenal androgens to dihydrotestosterone. Dihydrotestosterone still remaining in prostate tissue after androgen deprivation therapy may require new therapies such as treatment with a combination of 5α-reductase inhibitors and antiandrogens, as well as castration.**

INTRODUCTION

Since the observation of Huggins and Hodges (1) that disseminated prostate cancer reacts favorably to castration or the administration of estrogenic hormones, first-line hormonal therapy has been used to impair the production or activity of androgens or both.

Testosterone is converted to dihydrotestosterone by 5-α reductase in the prostate. There have been several reports that examined in detail the method for quantitative analysis of the tissue dihydrotestosterone concentrations of the prostate (2–5). Belanger *et al.* (5) and Labrie *et al.* (6) stated that after the elimination of testicular androgens, the intraprostatic concentration of dihydrotestosterone remains at ~40%. These data indicate that a substantial level of dihydrotestosterone remains in the prostate after castration. Belanger *et al.* (5) and Labrie *et al.* (6) also suggested that dihydrotestosterone completely disappears from the prostate after androgen deprivation therapy with castration and flutamide. The influence of androgen deprivation therapy on dihydrotestosterone levels in the prostatic tissue in prostate cancer, however, is not fully known. Changes in dihydrotestosterone levels in the prostatic tissue during androgen deprivation therapy for prostate cancer in the same patients have not been reported. One of the reasons is that the detectable quantity of dihydrotestosterone involved in the prostatic tissue collected from needle biopsy samples is minute. We, however, have developed a detection system for minuscule quantities of dihydrotestosterone with liquid chromatography/electrospray ionization-mass spectrometry after polar derivatization of dihydrotestosterone (7).

Therefore, we analyzed dihydrotestosterone levels in prostatic tissue and endogenous hormone levels in serum both in patients with prostate cancer and those without prostate cancer who underwent prostatic biopsy. The patients diagnosed with clinically localized prostate cancer, furthermore, were treated with androgen deprivation therapy in a neoadjuvant setting for 6 months. We then carried out rebiopsy or prostatectomy 6 months after androgen deprivation therapy treatment to analyze dihydrotestosterone levels in prostatic tissue and endogenous hormone levels in serum.

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PATIENTS AND METHODS

Patients. Between April 2000 and October 2002, 103 patients suspected of having prostate cancer underwent prostatic biopsy. Those patients diagnosed with clinically localized prostate cancer were given androgen deprivation therapy (castration and flutamide) in a neoadjuvant setting for 6 months. Baseline patients' characteristics are listed in Table 1. This research was reviewed and approved by the Institutional Review Board. Written informed consent was obtained from all participants.

Sample Collections. To determine dihydrotestosterone levels, the samples of prostatic tissue were obtained from the midlateral region of the prostate with a 16-gauge biopsy needle; alternatively, prostatectomy specimens were used. Serum samples for endocrine study were collected from the patients between 9:00 and 12:00 p.m. (noon). In all patients who underwent ultrasound-guided biopsy or radical prostatectomy, serum samples were obtained before the respective interventions. Serum samples were stored at −20°C until additionally processed. All biopsies and prostatectomy specimens were analyzed by conventional pathological examination. Tissue samples were stored at −80°C until additional processing.

Hormones and Prostate-specific Antigen Levels of Serum Samples Other Than Dihydrotestosterone. The prostate-specific antigen and hormones were quantified by commercially available immunoassays: prostate-specific antigen [TOSOH-II (PA)], luteinizing hormone, and follicle-stimulating hormone. All hormones were quantified by automated fluorescence polarization assays on Tosoh equipment (Tosoh Corporation, Tokyo, Japan). Serum levels of testosterone, adrenocorticotropic hormone (ACTH), cortisol, androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and prolactin were determined by radioimmunoassay (BML, Tokyo, Japan).

Sensitive Analysis of dihydrotestosterone in Prostatic Tissues and Serum Samples by Semi-Micro-Liquid Chromatography/Electrospray Ionization-Mass Spectrometry after Polar Derivatization. The dihydrotestosterone levels in prostatic tissue and serum were analyzed by liquid chromatography/electrospray ionization-mass spectrometry after polar derivatization of dihydrotestosterone, as described previously (7). The polar derivatization method for electrospray ionization was developed and applied to the sensitive analysis of dihydrotestosterone. Dihydrotestosterone in prostatic tissue was dissolved in alkaline solution and extracted via a solid-phase column and derivatized to *N*-methylpyridinium-dihydrotestosterone as a polar derivative. *N*-Methylpyridinium-dihydrotestosterone was purified by Bond Elut C18 and determined with a semi–micro-liquid chromatography/electrospray ionization-mass spectrometry with selected reaction monitoring. The calibration graph was linear from 5 to 100 pg/tube. The lowest dihydrotestosterone level in this method was 5 pg/tube.

Statistical Analysis. Statistical comparison of hormonal levels in patients with prostate cancer before treatment and noncancer patients at diagnosis was carried out with the Mann-Whitney *U* test. Statistical comparison of DHEA level in patients with prostate cancer before treatment and noncancer patients at diagnosis was also carried out with a multivariate analysis with logistic regression after forcing age in the model. Statistical comparison of the influence of androgen deprivation therapy on hormonal levels was carried out with the Wilcoxon's signed rank test. The correlation between the dihydrotestosterone levels or ACTH and ACTH or other androgens was analyzed with the Spearman rank correlation coefficient. The test was two-sided, and a P value of <0.05 was considered statistically significant. Statistical analyses were carried out with SPSS software v.11.0 for PC (SPSS, Inc., Chicago, IL).

RESULTS

Clinical Results. Sixty-nine patients were diagnosed as having prostate cancer and 34 as having a nonmalignant prostate condition. The patients' characteristics are listed in Table 1. Thirty of the 69 patients were treated with androgen deprivation therapy with a luteinizing hormone-releasing hormone agonist (goserelin acetate or leuprolide acetate) or bilateral orchiectomy and flutamide in a neoadjuvant setting for 6 months. Eight of the 30 patients were withdrawn from flutamide treatment because of adverse effects during the following dosing periods: 1 month, 1 patient; 2 months, 1 patient; 4 months, 3 patients; and 5 months, 3 patients. Six patients were withdrawn because of liver dysfunction and two because of diarrhea.

Table 1 Patient characteristics

	Total	With cancer	Without cancer
No. of patients	103	69	34
Age (y) at diagnosis [mean (range)]	69 (41–86)	71 (45–86)*	66 (41–81)*
PSA [ng/mL, median (range)]	14.9 (3.0–19578)	27.4 (4.7–19578)†	8.6 (3.0–27.8)†
Gleason score [mean (range)]		6 (4–10)	
M0		54	
M1		15	
Androgen deprivation therapy		30	
Age (y) at diagnosis [mean (range)]		71 (57–78)	
LH-RHa + flutamide		25	
Castration + flutamide		5	

Abbreviations: LH-RHa, luteinizing hormone-releasing hormone agonist.
* $P = 0.004$.
† $P < 0.001$.

Dihydrotestosterone Levels in Prostatic Tissue and Serum Hormone Levels in Patients with Prostate Cancer (n = 69) before Treatment and Noncancer Patients (n = 34) at Diagnosis. In this study, the serum DHEA level was significantly lower in patients with prostate cancer by comparison with noncancer patients using the Mann-Whitney U test (P = 0.037; Table 2). However, there is no statistical association between prostate cancer and DHEA level using results of the logistic regression model (P = 0.762). There were no statistically significant differences between the patients with prostate cancer and the patients without prostate cancer in LH (P = 0.165), follicle-stimulating hormone (P = 0.206), prolactin (P = 0.169), ACTH (P = 0.788), cortisol (P = 0.770), testosterone (P = 0.539), androstenedione (P = 0.509), and DHEA-S (P = 0.404), including dihydrotestosterone levels in serum (P = 0.602) and prostatic tissue (P = 0.302) in this study. There were no statistically significant differences between the patients with prostate cancer and the patients without prostate cancer with respect to the ratios of testosterone to serum dihydrotestosterone (P = 0.772) and dihydrotestosterone in prostatic tissue (P = 0.191).

Correlation between the Dihydrotestosterone Levels and Other Androgens in Patients with Prostate Cancer before Treatment and Noncancer Patients at Diagnosis (n = 103). The level of dihydrotestosterone in prostatic tissue before androgen deprivation therapy was not correlated with the serum level of testosterone (rs = 0.010, P = 0.923; Table 3). The level of dihydrotestosterone in prostatic tissue was correlated with the serum levels of DHEA (rs = 0.243, P = 0.014) and DHEA-S (rs = 0.239, P = 0.015). There was a small correlation between the serum level of dihydrotestosterone and the level of dihydrotestosterone in prostatic tissue (rs = 0.229, P = 0.025, y = 0.001x + 5.0165). The serum level of dihydrotestosterone was correlated with the serum levels of testosterone (rs = 0.425, P < 0.001) and DHEA (rs = 0.305, P = 0.003).

The Influence of Androgen Deprivation Therapy [Total (n = 30), 6 Months with Flutamide (n = 22), and Flutamide Withdrawal (n = 8)] on Hormone Levels. The serum levels of ACTH (P < 0.001), testosterone (P < 0.001), androstenedione (P < 0.001), DHEA (P = 0.001), DHEA-S (P < 0.001), and dihydrotestosterone (P < 0.001) and the level of dihydrotestosterone in prostatic tissue (P < 0.001) significantly declined after androgen deprivation therapy (Table 4). The dihydrotestosterone levels in prostatic tissue after androgen deprivation therapy, however, remained at ~25% of those measured before androgen deprivation therapy. The dihydrotestosterone levels in serum decreased to ~7.5% after androgen deprivation therapy. Testosterone levels decreased to ~2.7% after androgen deprivation therapy, and serum hormone levels were reduced to 59% for ACTH, 52% for androstendione, 60% for DHEA, and 64% for DHEA-S. The decrease in adrenal androgens in the flutamide withdrawal cases was less significant than that in the flutamide cases. The prolactin level (P = 0.737) and cortisol level (P = 0.148) in serum did not decline after androgen deprivation therapy.

Table 3 The correlation between the DHT levels and other androgens in patients with prostate cancer and noncancer patients at diagnosis (N = 103)

	sDHT	tDHT
Testosterone	rs = 0.425 P < 0.001	rs = 0.010 P = 0.923
Androstenedione	rs = 0.254 P = 0.130	rs = 0.019 P = 0.852
DHEA	rs = 0.305 P = 0.003	rs = 0.243 P = 0.014
DHEA-S	rs = 0.065 P = 0.530	rs = 0.239 P = 0.015
sDHT		rs = 0.229 P = 0.025
tDHT	rs = 0.229 P = 0.025	

Abbreviations: sDHT, dihydrotestosterone level in serum; tDHT, dihydrotestosterone level in prostatic tissue.

Correlation between the Dihydrotestosterone Levels or ACTH and ACTH or Other Androgens after androgen deprivation therapy. The level of dihydrotestosterone in prostatic tissue was correlated with the serum level of testosterone (rs = 0.390, P = 0.033; Table 5). The level of dihydrotestos-

Table 2 Pretreatment serum hormones

	Patients with cancer Mean (SD)	Patients without cancer Mean (SD)	P	Logistic regression analysis P	Odds ratio	95% confidence interval
Age (y)	71 (45–86)	66 (41–81)	0.004	0.015	0.928	0.874–0.986
LH (mIU/mL)	6.6 (5.8)	4.61 (2.5)	0.165			
FSH (mIU/mL)	20.0 (19.4)	12.8 (6.0)	0.206			
PRL (ng/mL)	10.5 (18.4)	7.0 (3.4)	0.169			
ACTH (pg/mL)	42.7 (34.2)	44.3 (34.7)	0.788			
Cortisol (μg/dL)	15.3 (5.5)	15.6 (4.6)	0.770			
Testosterone (ng/dL)	449.3 (170.5)	425.0 (133.0)	0.539			
Androstene dione (ng/mL)	0.81 (0.41)	0.86 (0.41)	0.509			
DHEA (ng/mL)	1.79 (1.26)	2.26 (1.35)	0.037	0.762	1.058	0.734–1.524
DHEA-S (ng/mL)	1169.8 (803.3)	1263.0 (876.4)	0.404			
sDHT (pg/mL)	462.5 (274.6)	423.9 (243.2)	0.602			
tDHT (ng/g tissue)	5.19 (2.50)	5.61 (1.96)	0.302			
Testosterone/sDHT	1.27 (1.00)	1.07 (0.59)	0.772			
Testosterone/tDHT	99.5 (67.8)	78.9 (44.5)	0.191			

Abbreviations: sDHT, dihydrotestosterone level in serum; tDHT, dihydrotestosterone level in prostatic tissue.

Table 4 The influence of ADT [total (N = 30), 6 months with flutamide (N = 22), and flutamide withdrawal (N = 8)] on hormone levels

	Before ADT Mean (SD)	After ADT (N = 30) Mean (SD) P	6 months with flutamide (N = 22) Mean (SD) P	Flutamide withdrawal (N = 8) Mean (SD) P
PRL (ng/mL)	8.2 (4.0)	7.6 (2.3)	8.2 (2.3)	8.4 (5.3)
		0.737	0.709	0.208
ACTH (pg/mL)	48.3 (46.0)	28.3 (12.1)	28.2 (13.7)	28.4 (6.2)
		<0.001	0.009	0.327
Cortisol (μg/dL)	15.3 (4.5)	15.6 (5.2)	15.9 (4.5)	13.7 (5.5)
		0.148	0.182	0.715
Testosterone (ng/dL)	460.8 (192.4)	12.4 (6.8)	10.4 (5.4)	18.0 (7.6)
		<0.001	<0.001	0.012
Androstenedione (ng/mL)	0.81 (0.36)	0.42 (0.22)	0.38 (0.21)	0.52 (0.24)
		<0.001	<0.001	0.025
DHEA (ng/mL)	2.03 (1.32)	1.22 (0.76)	1.06 (0.56)	1.64 (1.09)
		0.001	0.001	0.484
DHEA-S (ng/mL)	1194.9 (855.0)	761.3 (875.6)	654.7 (505.7)	1054.0 (994.9)
		<0.001	<0.001	0.123
sDHT (pg/mL)	503.4 (315.9)	38.0 (31.2)	33.0 (27.0)	51.8 (39.3)
		<0.001	<0.001	0.012
tDHT (ng/g tissue)	5.44 (2.84)	1.35 (1.32)	1.23 (1.47)	1.69 (0.77)
		<0.001	<0.001	0.036

Abbreviations: ADT, androgen deprivation therapy; sDHT, dihydrotestosterone level in serum; tDHT, dihydrotestosterone level in prostatic tissue.

terone in prostatic tissue was not correlated with the serum level of androgens other than testosterone. The serum level of dihydrotestosterone was correlated with the serum levels of androstenedione (rs = 0.466, P = 0.009), DHEA (rs = 0.577, P = 0.001), and DHEA-S (rs = 0.480, P = 0.007). There was no correlation between the serum level of dihydrotestosterone and the level of dihydrotestosterone in prostatic tissue (rs = 0.013, P = 0.869). There was no correlation between the serum level of ACTH and the serum levels of androgens and the level of dihydrotestosterone in prostatic tissue.

DISCUSSION

Our results showed that after androgen deprivation therapy with castration and flutamide, the dihydrotestosterone level in prostatic tissue remained at ~25% of the amount measured before androgen deprivation therapy in the same patients. Previous reports revealed that the mean dihydrotestosterone levels in the prostate tissue treated with androgen deprivation therapy were between 10 and 40% of those of untreated prostrate tissue (2–5). Mohler *et al.* (8) showed that the dihydrotestosterone level in recurrent prostate cancer tissue was decreased to 18% of the level in benign prostate tissue. Belanger *et al.* (5) and Labrie *et al.* (6) indicated that androgen deprivation therapy with castration and flutamide decreases intraprostatic dihydrotestosterone to the point where it is undetectable. Our data, however, indicates that flutamide acts to suppress the binding of the residual dihydrotestosterone to androgen receptors, not to decrease intraprostatic dihydrotestosterone to undetectable levels.

It is not clear to what extent the testosterone and dihydrotestosterone in prostate tissue derives from adrenal androgens or other steroid precursors. Previous reports showed that persistent levels of prostatic dihydrotestosterone after castration are derived from adrenal androgens in the prostate (3, 5, 8). A sulfatase is present in human prostate that converts DHEA-S to DHEA (9). The plasma concentration of DHEA-S is 100 to 500 times higher than that of testosterone. Koh *et al.* (10, 11) revealed that prostate cancer cells have the ability to convert adrenal androgens to dihydrotestosterone intracellularly. Mohler *et al.* (8) revealed that recurrent prostate cancer tissue levels of adrenal androgens were ~50% the levels in benign prostate. In our data, the level of dihydrotestosterone in prostatic tissue before androgen deprivation therapy was not correlated with the serum level of testosterone (Table 3). The level of dihydrotestosterone in prostatic tissue after androgen deprivation therapy was only correlated with the serum level of testosterone (Table 5). The level of dihydrotestosterone in prostatic tissue before androgen deprivation therapy was correlated with the serum level of adrenal androgens other than androstenedione (Table 3). The serum dihydrotestosterone level after androgen deprivation

Table 5 The correlation between the DHT levels or ACTH and ACTH or other androgens after androgen deprivation therapy (N = 30)

	sDHT	tDHT	ACTH
ACTH	rs = 0.103	rs = 0.347	
	P = 0.586	P = 0.060	
Testosterone	rs = 0.260	rs = 0.390	rs = −0.014
	P = 0.165	P = 0.033	P = 0.942
Androstenedione	rs = 0.466	rs = 0.351	rs = 0.326
	P = 0.009	P = 0.057	P = 0.079
DHEA	rs = 0.577	rs = 0.071	rs = 0.080
	P = 0.001	P = 0.708	P = 0.674
DHEA-S	rs = 0.480	rs = 0.341	rs = 0.017
	P = 0.007	P = 0.065	P = 0.930
sDHT		rs = −0.013	rs = 0.103
		P = 0.869	P = 0.586
tDHT	rs = −0.013		rs = 0.347
	P = 0.869		P = 0.060

Abbreviations: sDHT, dihydrotestosterone level in serum; tDHT, dihydrotestosterone level in prostatic tissue.

therapy was correlated with serum levels of adrenal androgen (Table 5). These findings suggest that serum testosterone after androgen deprivation therapy mostly comes from adrenal androgens converted in the prostatic cells. These findings could also suggest that serum dihydrotestosterone after androgen deprivation therapy comes from adrenal androgens converted in the peripheral tissues, including the prostate. It is possible that the prostate is the major dihydrotestosterone-producing organ, and the level of dihydrotestosterone in prostatic tissue is correlated with the level of adrenal androgens and testosterone in prostatic tissue. These results reveal that the source of dihydrotestosterone in prostatic tissue after androgen deprivation therapy involves intracrine production within the prostate to convert adrenal androgens to dihydrotestosterone.

The serum hormone levels were reduced to ~60% in ACTH, androstenedione, DHEA, and DHEA-S after androgen deprivation therapy with castration and flutamide in our study. The mechanism causing the decrease of adrenal androgens after androgen deprivation therapy has yet to be determined (12–14). Several investigators have shown the effects of flutamide on the plasma levels of adrenal androgens (12, 14). Flutamide allegedly decreases adrenal androgens after treatment by castration and flutamide (13, 14). Our results also showed that castration and flutamide reduced adrenal androgens to ~60%. The serum ACTH level after androgen deprivation therapy was not correlated with serum adrenal androgen levels and dihydrotestosterone levels in serum and prostatic tissue. Prolactin and cortisol in serum did not decline after androgen deprivation therapy. The mechanism of the suppression of adrenal androgens is speculated to be by flutamide having an inhibitory effect on human adrenal microsomal 17α-hydroxylase and 17,20-lyase activities (14).

A recent collaborative meta-analysis has shown that the addition of a nonsteroidal antiandrogen (flutamide or nilutamide) to castration reduced highly significantly the risk of death (all causes of death) by 8% (95% confidence interval, 3–13; $P = 0.005$), which translates to a small but significant improvement in 5-year survival of 2.9% over castration alone (15). Most meta-analyses show a positive result with nonsteroidal antiandrogens (16). The percentage of PSA responses has been shown to be significantly higher among patients receiving androgen deprivation therapy composed of castration and flutamide than among patients undergoing castration only (17). Labrie *et al.* (18) showed long-term and continuous androgen deprivation therapy could offer the possibility of long-term control or possible cure of localized prostate cancer. It is established that 5α-reductase inhibitor such as finasteride can reduce intraprostatic levels of dihydrotestosterone (19). Visakorpi *et al.* (20) showed that amplification of the androgen receptor gene is increased during androgen deprivation therapy. Gregory *et al.* (21) showed that the androgen receptor is transcriptionally active in recurrent prostate cancer and can increase cell proliferation at the low levels of androgen that occur after androgen deprivation therapy. Zegarra-Moro *et al.* (22) revealed that therapies that target the androgen receptor directly with an androgen receptor antibody or androgen receptor ribozymes inhibited growth of both androgen-sensitive and androgen-refractory prostate cancer *in vitro*. Chen *et al.* (23) revealed that the increase in androgen receptor mRNA and protein was both necessary and sufficient to convert prostate cancer growth from a hormone-sensitive to a hormone-refractory stage and was dependent on a functional ligand-binding domain. Increased levels of androgen receptor confer resistance to antiandrogens by amplifying signal output from low levels of residual ligand and by altering the normal response to antagonists (23). Leibowitz and Tucker (24) revealed that triple androgen blockade therapy followed by finasteride maintenance appears to be a promising alternative for the management of patients with clinically localized or locally advanced prostate cancer. These findings and our results suggest that new therapies that target androgen receptor and prevent formation of androgens within prostate cancer cells such as treatment with a combination of antiandrogens and 5α-reductase inhibitors can block the stimulation from adrenal androgens that contributes ~25% of total dihydrotestosterone when they are combined with testicular suppression of androgens and may offer the most effective androgen deprivation therapy to prolong remission of prostate cancer as of now.

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Characteristics of Patients with Prostate Cancer Who Have Initially been Treated by Hormone Therapy in Japan: J-CaP Surveillance

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Objective: Hormone therapy for prostate cancer has empirically prevailed in Japan. We planned to evaluate the trends and outcome of hormone therapy for establishing an adequate guideline.

Methods: Patients with prostate cancer who were initially treated by hormone therapy were registered through the J-CaP registration system. This report summarizes the background factors.

Results: From January 2001 to October 2003, 17 872 patients were registered from 395 institutes throughout Japan. The background factors of 17 312 patients were analyzed. The 17 872 patients were estimated as composing more than half of newly diagnosed prostate cancer patients in Japan. Of these, 22.9, 35.1, 32.9 and 8.6% belonged to T1, T2, T3 and T4, respectively. For the purposes of hormone therapy, 77.5% was primary hormone therapy. Neoadjuvant setting and adjuvant setting were 18.1 and 4.3%, respectively. About 60% of the hormone therapy was combined hormone therapy with LH-RHa plus anti-androgens.

Conclusion: Irrespective of patients' age, TNM, stage of illness, or histological background, the majority of prostate cancer patients in Japan are receiving hormone therapy. It is necessary to evaluate whether this trend is merely a continuation of past experience of Japanese urologists or if there is a difference in the profile of effect and side-effect in the case of Japanese patients compared to therapy given in Westerners.

Key words: prostate cancer – hormone therapy – endocrine therapy

INTRODUCTION

In prostate cancer treatment, hormone therapy has been used in Europe and North America mainly to provide temporary relief for advanced cancers. However, the CaPSURE report (1), released in 2003, indicates that there is a rapid increase in the use of hormone therapy on localized cancer in the United States, which suggests a drastic change in the role of hormone therapy. Meanwhile, in Japan, hormone therapy has been used over many years in a considerable number of patients with localized or locally advanced prostate cancer. In recent years, while clinical trial data (2,3) indicating its usefulness have been accumulating, the outcomes have yet to be accurately analyzed. As typically seen in the early prostate cancer (EPC) studies of recent years in Europe and North America (4), clinical trials are being reported that point to the effectiveness of hormone therapy in localized cancer (5,6). Against this backdrop, in 2001 the Japan Study Group of Prostate Cancer (J-CaP Study Group) was inaugurated with financial support from the Japan Kidney Foundation. This project has been authorized by the Japan Urological Association. The purposes of this study group were to gather information about the hormone therapy administered to Japanese prostate cancer patients living in Japan and to analyze the outcomes of treatment in order to create a guideline for optimal hormone therapy. This report summarizes the background factors of patients receiving hormone therapy across most of Japan.

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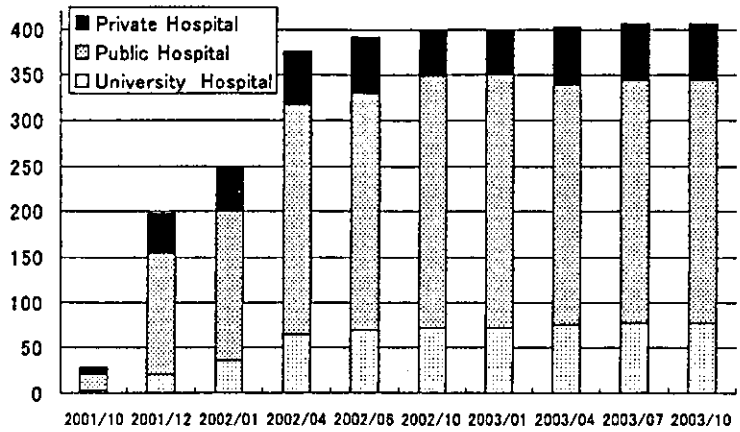

Figure 1. Overview of the year of registration and type of institution.

PATIENTS AND METHODS

The rules for the J-CaP study group are summarized in the Appendix.

Eligible Institutions

Eligible institutions are Japanese urological institutions endorsing the purpose of this study that are able to obtain the approval of their own ethics committees (or IRB). Institutions that have not yet established their own ethics committee (or IRB) but can be vetted instead by an affiliated institution or can obtain approval from the person responsible for the institution are also included. As a rule, in each eligible institution, all cases of patients newly starting hormone therapy for prostate cancer in and after January 2001 will be regarded as subjects of the study.

Period of Research

Registration will commence when approval is obtained from the J-CaP Study Group. The term of case registration is for 3 years and the follow-up period is for 2 years.

Method

Data under the following headings for each registered case will be relayed to the secretariat server over the Internet: date of birth, family history, date of PSA reading, PSA value, PSA kit name, testosterone value, biopsy date, Gleason score, histological grade, clinical stage, case history, details of hormone therapy, whether or not there has been progress observation, whether or not surgery was carried out, date of surgery, operative procedure, whether or not radiotherapy is being conducted, irradiation method, irradiation date, progress. TNM classification used was the 5th edition (7). Histological grade and other criteria were adopted in accordance with the Japanese Urological Association/Japan Society of Pathology 3rd Edition of General Rules for Clinical and Pathological Studies on Prostate Cancer (8).

Follow-up Method

The registered cases, as a rule, are to be updated once every 3 months with regard to test data, change in treatment and progress data. The secretariat immediately contacts institutions not updating information, requesting data input. The secretariat forwards input forms for data addition, and confirms registered cases as of that date as necessary. Additionally, assistance can be given on adding test data and entering changes in treatment and progress data.

This report concerns patient background factors, tumor factors and treatment details of registered cases between 2001 and October 2003.

RESULTS

Participating Institutions

By October 2003, 395 institutions throughout Japan had registered, acquiring IDs and passwords. Eleven institutions of the 395 later withdrew registration. Fig. 1 gives an overview of the year of registration and type of institution. The number of university hospitals registering was 76 (60.2% of university hospitals in Japan); in detail, 35 national university hospitals (83.3%) have been included.

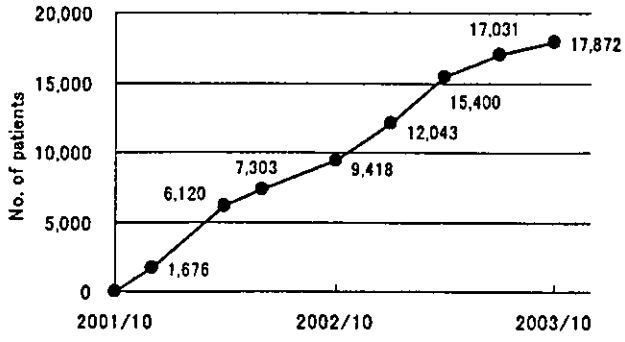

Figure 2. Cumulative number of patients registered.

Table 1. Patient backgrounds; family history of prostate cancer, age at diagnosis and PSA value at diagnosis

	2001	2002	2003	Total	%
Family history					
No history	5959	6104	1771	13 834	79.9
Within 2nd degree of relationship	120	128	29	277	1.6
Within 3rd degree of relationship	11	8	3	22	0.1
Don't know	1412	1453	314	3179	18.4
Total	7502	7693	2117	17 312	100.0
Age at diagnosis					
<60	329	320	61	710	4.1
60–64	596	620	161	1377	8.0
65–69	1197	1265	331	2793	16.1
70–74	1935	2037	567	4539	26.2
75–79	1798	1889	562	4249	24.5
≥80	1647	1562	435	3644	21.0
Total	7502	7693	2117	17 312	100.0
PSA at diagnosis					
<4	255	269	73	597	3.4
4–<10	1680	1863	556	4099	23.7
10–<20	1470	1628	493	3591	20.7
20–<50	1459	1514	387	3360	19.4
≥50	2612	2401	606	5619	32.5
No description	26	18	2	46	0.3
Total	7502	7693	2117	17 312	100.0

Number of Registered Patients

As shown in Fig. 2, 17 872 patients were registered by October 2003. This survey investigated patients who were first diagnosed with prostate cancer at the registered institutions during this period. Respectively, 7952 and 8195 new patients were reported in 2001 and 2002 by 246 and 216 institutions. Of these new patients, 5969 and 6064 were newly administered hormone therapy, and 5646 and 5651 were registered with J-CaP. In summary, it is shown that 75% of new patients were given hormone therapy in some form and 70% registered with J-CaP.

Patient Background Factors

Of the 17 872 registered patients at the time of data compilation, data were collected from 17 312 patients. 529 cases without any record of hormone therapy commencement date were excluded, as were 31 cases whose therapy was reported as commencing in 2000. Family history, age at diagnosis and PSA value at diagnosis are given in Table 1.

Tumor Background Factors

A summary of Gleason score, histological grade, TNM classification and clinical stage (TNM) is given in Table 2.

Table 2. Tumor backgrounds; Gleason score, histological grade, TNM classification, TNM clinical stage

	2001	2002	2003	Total	%
Gleason score					
2–4	654	551	150	1355	7.8
5	696	744	251	1691	9.8
6	1029	1250	401	2680	15.5
7	1595	1958	579	4132	23.9
8–10	1801	2337	590	4728	27.3
No description	1727	853	146	2726	15.7
Total	7502	7693	2117	17 312	100.0
Histological differentiation					
Well	1489	1554	453	3496	20.2
Moderate	3360	3362	990	7712	44.5
Poor	1995	1997	513	4505	26.0
Unknown	103	119	16	238	1.4
No description	555	661	145	1361	7.9
Total	7502	7693	2117	17 312	100.0
T stage					
T0	1	3	0	4	0.0
T1	1630	1813	518	3961	22.9
T2	2566	2680	832	6078	35.1
T3	2597	2509	589	5695	32.9
T4	673	657	157	1487	8.6
Tx	27	25	12	64	0.4
No description	8	6	9	23	0.1
Total	7502	7693	2117	17 312	100.0
N factor					
N0	6000	6315	1767	14 082	81.3
N1	1004	917	210	2131	12.3
Nx	462	427	119	1008	5.8
No description	36	34	21	91	0.5
Total	7502	7693	2117	17 312	100.0
M factor					
M0	5380	5696	1634	12 710	73.4
M1	157	119	12	288	1.7
M1a	83	77	11	171	1.0
M1b	1496	1428	327	3251	18.8
M1c	100	71	19	190	1.1
Mx	250	268	93	611	3.5
No description	36	34	21	91	0.5
Total	7502	7693	2117	17 312	100.0
Clinical stage					
II	3684	3987	1188	8859	51.2
II	1273	1327	326	2926	16.9
IV	2082	1945	444	4471	25.8
No description	463	434	159	1056	6.1
Total	7502	7693	2117	17 312	100.0

Table 3. Purpose of hormone therapy

	2001	2002	2003	Total	%
Hormonal therapy					
Main	5926	5914	1585	13 425	77.5
Adjuvant	306	366	81	753	4.3
Neoadjuvant	1270	1413	451	3134	18.1
Total	7502	7693	2117	17 312	100.0
Hormonal therapy detail					
Orchiectomy only	236	214	63	513	3.0
Orchiectomy + medication	605	427	96	1128	6.5
LH-RHa only	826	1065	319	2210	12.8
LH-RHa + anti-androgen	4431	4703	1249	10 383	60.0
Anti-androgen only	392	584	251	1227	7.1
Other	1012	700	139	1851	10.7
Total	7502	7693	2117	17 312	100.0

HORMONE THERAPY

As to the reason for hormone therapy, primary application of hormone therapy was the most prevalent, comprising 77.5% of the total, followed by 18.1% neoadjuvant and 4.3% adjuvant (Table 3).

Table 3 also indicates an overview of the types of hormone therapy. The combined use of LH-RHa + anti-androgen drug is the largest, comprising 60%. Anti-androgen monotherapy was 7.1% and LH-RHa monotherapy was 12.8%.

Table 4 shows the relations between the purpose of hormone therapy and T category, clinical stage, Gleason score and age. A notable feature is that in all categories, primary use of hormone therapy was the most common.

Table 5 shows the relations between the type of hormone therapy and T category, clinical stage, Gleason score and age. In all categories and ages, combined androgen blockade (CAB) was used in the main. In Table 6, details are given of the main treatment methods when hormone therapy was administered as neoadjuvant, as well as the details of main treatment methods when used as adjuvant.

COMPLIANCE OF SURVEY DATA

Omission of data entry among registered data included 0.2% of patients for whom PSA values were not recorded. Meanwhile, omission of histological grade accounted for 7.8% and omission of clinical stage 6.1%. As for Gleason score, 23% of registered cases in 2001 had no entry, but in 2002 this had decreased to 11.9% and by 2003, to 6.5%. This is thought to be because in the First Edition of the Japanese Urological Association and Japan Society of Pathology's General Rules for Clinical and Pathological Studies on Prostate Cancer, Gleason score entry was not compulsory. Only in the Second Edition did Gleason score become required.

Table 4. Relations between the purpose of hormone therapy and T category, TNM clinical stage, Gleason score and patient age

	Main	Adjuvant	Neoadjuvant	Total	%
T stage					
T0	4 (0.1%)			4	0.0
T1	2689 (67.9%)	218 (5.5%)	1054 (26.6%)	3961	22.9
T2	4260 (70.1%)	333 (5.5%)	1485 (24.4%)	6078	35.1
T3	4965 (87.2%)	174 (3.1%)	556 (9.8%)	5695	32.9
T4	1425 (95.8%)	26 (1.7%)	36 (2.4%)	1487	8.6
Tx	60 (93.8%)	2 (3.1%)	2 (3.1%)	64	0.4
No description	22 (95.7%)		1 (4.3%)	23	0.1
Total	13 425 (77.5%)	753 (4.3%)	3134(18.1%)	17 312	100.0
Clinical stage					
II	5847 (66.0%)	537 (6.1%)	2475 (27.9%)	8859	51.2
III	2263 (77.3%)	145 (5.0%)	518 (17.7%)	2926	16.9
IV	4362 (97.6%)	44 (1.0%)	65 (1.5%)	4471	25.8
No description	953 (90.2%)	27 (2.6%)	76 (7.2%)	1056	6.1
Total	13 425 (77.5%)	753 (4.3%)	3134 (18.1%)	17 312	100.0
Gleason score					
2–4	996 (73.5%)	69 (5.1%)	290 (21.4%)	1355	7.8
5	1214 (71.8%)	91 (5.4%)	386 (22.8%)	1691	9.8
6	1902 (71.0%)	120 (4.5%)	658 (24.6%)	2680	15.5
7	3179 (76.9%)	175 (4.2%)	778 (18.8%)	4132	23.9
8–10	3966 (83.9%)	185 (3.9%)	577 (12.2%)	4728	27.3
Unknown	2168 (79.5%)	113 (4.1%)	445 (16.3%)	2726	15.7
Total	13 425 (77.5%)	753 (4.3%)	3134 (18.1%)	17 312	100.0
Age at diagnosis					
<60	364 (51.3%)	48 (6.8%)	298 (42.0%)	710	4.1
60–64	767 (55.7%)	95 (6.9%)	515 (37.4%)	1377	8.0
65–69	1613 (57.8%)	234 (8.4%)	946 (33.9%)	2793	16.1
70–74	3305 (72.8%)	226 (5.0%)	1008 (22.2%)	4539	26.2
75–79	3808 (89.6%)	116 (2.7%)	325 (7.6%)	4249	24.5
≥80	3568 (97.9%)	34 (0.9%)	42 (1.2%)	3644	21.0
Total	13 425 (77.5%)	753 (4.3%)	3134 (18.1%)	17 312	100.0

FOLLOW-UP DATA

For approximately 92% of the registered cases in 2001 and 75% of the registered cases in 2002, the input of follow-up data was confirmed at least once. The period (median) from the start of hormone therapy to the latest follow-up data entry was 406 days (between 0 and 964) for 2001-registered cases and 189 (between 0 and 615) for 2002-registered cases.

DISCUSSION

In Japan, the General Rules for Clinical and Pathological Studies on Prostate Cancer issued by the Japanese Urological Association and Japan Society of Pathology were first published in

Table 5. Relations between the type of hormone therapy and T category, TNM clinical stage, Gleason score and patient age

	Orchiectomy only	Orchiectomy + medication	LH-RHa only	LH-RHa + anti-androgen	Anti-androgen only	Other	Total	%
T stage								
T0				1 (25.0%)	1 (25.0%)	2 (50.0%)	4	0.0
T1	112 (2.8%)	169 (4.3%)	719 (18.2%)	2333 (58.9%)	427 (10.8%)	201 (5.1%)	3961	22.9
T2	158 (2.6%)	277 (4.6%)	921 (15.2%)	3737 (61.5%)	532 (8.8%)	453 (7.5%)	6078	35.1
T3	196 (3.4%)	466 (8.2%)	490 (8.6%)	3513 (61.7%)	215 (3.8%)	815 (14.3%)	5695	32.9
T4	44 (3.0%)	208 (14.0%)	69 (4.6%)	752 (50.6%)	46 (3.1%)	368 (24.7%)	1487	8.6
Tx	1 (1.6%)	5 (7.8%)	8 (12.5%)	36 (56.3%)	4 (6.3%)	10 (15.6%)	64	0.4
No description	2 (8.7%)	3 (13.0%)	3 (13.0%)	11 (47.8%)	2 (8.7%)	2 (8.7%)	23	0.1
Total	513 (3.0%)	1128 (6.5%)	2210 (12.8%)	10 383 (60.0%)	1227 (7.1%)	1851 (10.7%)	17 312	100.0
Clinical stage								
II	262 (3.0%)	360 (4.1%)	1527 (17.2%)	5366 (60.6%)	841 (9.5%)	503 (5.7%)	8859	51.2
III	111 (3.8%)	157 (5.4%)	325 (11.1%)	1959 (67.0%)	135 (4.6%)	239 (8.2%)	2926	16.9
IV	115 (2.6%)	559 (12.5%)	246 (5.5%)	2449 (54.8%)	132 (3.0%)	970 (21.7%)	4471	25.8
No description	25 (2.4%)	52 (4.9%)	112 (10.6%)	609 (57.7%)	119 (11.3%)	139 (13.2%)	1056	6.1
Total	513 (3.0%)	1128 (6.5%)	2210 (12.8%)	10 383 (60.0%)	1227 (7.1%)	1851 (10.7%)	17 312	100.0
Gleason score								
2–4	31 (2.3%)	54 (4.0%)	187 (13.8%)	820 (60.5%)	157 (11.6%)	106 (7.8%)	1355	7.8
5	65 (3.8%)	91 (5.4%)	247 (14.6%)	1032 (61.0%)	152 (9.0%)	104 (6.2%)	1691	9.8
6	80 (3.0%)	146 (5.4%)	468 (17.5%)	1579 (58.9%)	241 (9.0%)	166 (6.2%)	2680	15.5
7	151 (3.7%)	247 (6.0%)	557 (13.5%)	2515 (60.9%)	267 (6.5%)	395 (9.6%)	4132	23.9
8–10	119 (2.5%)	445 (9.4%)	373 (7.9%)	2796 (59.1%)	232 (4.9%)	763 (16.1%)	4728	27.3
Unknown	67 (2.5%)	145 (5.3%)	378 (13.9%)	1641 (60.2%)	178 (6.5%)	317 (11.6%)	2726	15.7
Total	513 (3.0%)	1128 (6.5%)	2210 (12.8%)	10 383 (60.0%)	1227 (7.1%)	1851 (10.7%)	17 312	100.0
Age at diagnosis								
<60	5 (0.7%)	32 (4.5%)	76 (10.7%)	413 (58.2%)	65 (9.2%)	119 (16.8%)	710	4.1
60–64	11 (0.8%)	88 (6.4%)	176 (12.8%)	816 (59.3%)	120 (8.7%)	166 (12.1%)	1377	8.0
65–69	57 (2.0%)	175 (6.3%)	319 (11.4%)	1674 (59.9%)	239 (8.6%)	329 (11.8%)	2793	16.1
70–74	96 (2.1%)	248 (5.5%)	564 (12.4%)	2826 (62.3%)	300 (6.6%)	505 (11.1%)	4539	26.2
75–79	153 (3.6%)	302 (7.1%)	566 (13.3%)	2556 (60.2%)	259 (6.1%)	413 (9.7%)	4249	24.5
≥80	191 (5.2%)	283 (7.8%)	509 (14.0%)	2098 (57.6%)	244 (6.7%)	319 (8.8%)	3644	21.0
Total	513 (3.0%)	1128 (6.5%)	2210 (12.8%)	10 383 (60.0%)	1227 (7.1%)	1851 (10.7%)	17 312	100.0

1985 (9) and this set of rules has been widely used ever since. The document gives a guideline on diagnosis and a detailed description of rules associated with making entries on patient background, tumor background and treatment method. Most of the papers presented at such meetings, such as the academic conference of the Urological Association, follow these rules and their diffusion rate is extremely high. The J-CaP survey basically followed the rules, and the accuracy of TNM diagnoses and clinical stage diagnoses is considered to be high. The Japanese Urological Association started a prostate cancer registration system from 2001, in accordance with these rules. However, this system is a registration of all prostate cancers. Therefore, when, for example, focusing on hormone therapy, we cannot necessarily expect satisfactory outcome data.

The morbidity of prostate cancer in Japan has been remarkably lower than in Europe and North America (10). Furthermore, due to anxieties about radiotherapy and the slowness of the introduction of technical expertise in radical prostatectomy, in many cases surgical castration or estrogen administration has been conducted across the board (11). However, in recent years Japan has seen an overwhelming increase in morbidity and mortality from prostate cancer (10). Compounding this, the influx of information about prostate and surgical techniques from Europe and North America has led to a rapidly growing debate on the method of treatment. Naturally, the trend towards newer treatment is beginning with reference to European (12) and North American guidelines (13) and the trend is set to continue.

Table 6. Main treatment for adjuvant or neoadjuvant hormone therapy

	Method	2001	2002	2003	Total
Operation					
Hormonal therapy followed by surgery	Retropubic	1609	18		1627
	Laparoscopic	23			23
	Perineal	17			17
	Other	3			3
	Total	1652	18		1670
Surgery followed by hormonal therapy	Retropubic	256	3		259
	Laparoscopic	10			10
	Perineal	2			2
	Other	2			2
	Total	270	3		273
Irradiation					
Hormonal therapy followed by irradiation	External beam	647	468	69	1184
	External + brachytherapy	15	4		19
	Brachytherapy	12	6	1	18
	Other	11	6	1	118
	Total	685	484	71	1339
Irradiation followed by hormonal therapy	External beam	46	62	10	118
	External + brachytherapy	3			3
	Brachytherapy	1	3		4
	Other	1	1		2
	Total	51	66	10	127

At present, with financial assistance from the Ministry of Health, Labor and Welfare, the Japanese Urological Association is working on the drafting of a prostate cancer treatment guideline at the earliest possible date. What is of concern here is that, in addition to the circumstances previously mentioned, there have been very few clinical trials with strong evidence carried out in this country. This causes a desperate lack in clinical data specific to Japan, which is essential to establish such a guideline. Hormone therapy in Japan, which has been administered only empirically, should be re-examined correctly to determine what outcome it is actually providing for the patients. Otherwise, it is likely that Japan's treatment guideline will become a reproduction of those of Europe and North America. Ethnic and philosophical differences, religious background, differences in perceptions about sex, and economic background—these diverse factors must be taken into account in the drafting of the most appropriate guideline for a country. The general attitude toward hormone therapy in Japan is similar to other East Asian countries (14). The recent treatment and clinical trial findings on hormone therapy in Europe and North America aimed at achieving long-term stable results indicate that we should examine the outcome of hormone therapy not only in Japan but throughout the world (4–6). The CaPSURE data reported in 2003 (1) consists of the analyses of 3439 cases, showing that the proportion of primary hormone treatment on localized prostate cancer rose dramatically from 4.6% in 1989 to 14.2% in 2001 and pointed firmly to the need to review the existing guidelines.

The institutions registered with J-CaP cover 60.2% of all university hospitals. According to Japan Cancer Statistics 2003, the number of patients newly diagnosed with prostate cancer in 1998 was 15 814 (15). In view of the proportion of J-CaP registered patients obtained in the survey of new patient numbers mentioned earlier, ~50% of new prostate cancer patients were treated by hormone therapy and registered with J-CaP. J-CaP had requested reports on the number of newly diagnosed prostate cancer patients in the registered institutions. Out of 358 institutions, 246 had responded as of 2001. Based on this report, 7952 patients were newly diagnosed with prostate cancer in those 246 institutions. Of these, 5969 patients (75.1%) were treated by hormone therapy in some form. Among those patients, 5646 (71%) were registered with J-CaP. In other words, 94.6% of the patients who had initiated a hormone therapy in 2001 were registered with J-CaP. This figure is almost the same in 2002. This illustrates the breadth of significance of this study. Patient background factors and PSA values at diagnosis would not represent the general trend because of the bias that patients registered for this study are receiving hormone therapy for the first time. However, we should make a special note of the low frequency of familial prostate cancer.

For the same reason, the background to the tumor in this report would not represent the overall trend of prostate cancer in Japan. Nevertheless, considering the finding that an extremely large number of patients are receiving hormone therapy, we can safely say that they express the overall background factors of prostate cancer in Japan to a fairly high degree of accuracy.

The analysis of the purpose and types of hormone therapy shows that there is a distinctively different trend in Japan compared to Europe or North America. These are the first findings in Japan based on a large-scale organized survey. To summarize: (i) many patients are receiving hormone therapy irrespective of age, TNM, stage of illness or histological background; (ii) more than 70% of them are under primary hormone therapy; and (iii) roughly 60% undergo combined androgen blockade (CAB). Since no clear outcome investigation has yet been carried out, we should evaluate this present status of hormone therapy in Japan either as: (i) it is merely a continuation of past experience, and in the near future, it should be managed carefully by adopting European and American guidelines; or (ii) it is still difficult to judge whether the effect of hormone therapy for Japanese patients is different in the profile of effects and side-effects from that for Westerners. What is more, in T2 treatment no accurate randomized study has been conducted so far globally on whether surgical treatment and radiotherapy are truly more effective than hormone therapy. Therefore, on this point we must reserve any conclusions.

The NCI–PDQ (13) and EAU guidelines (12) attach virtually no significance to hormone therapy on T2 prostate cancer. As for T3, the emphasis is on its significance as neoadjuvant before radiotherapy and little importance is assigned to the sole application of hormone therapy. Even when there is metastasis, there is debate on whether immediate hormone therapy is appropriate and also on whether there is any point in CAB; however, no clear conclusions have been reached (16,17).

In such circumstances, there are two clinical trial results in Japan reported recently that are extremely interesting. The first (2) is the results of a randomized study on hormone therapy given to localized or locally advanced prostate cancer. This was a comparative trial of LH-RHa + chlormadinone acetate (CMA) versus LH-RHa alone on patients in whom radical prostectomy was not chosen as treatment for whatever reason. The results are interim, with an observation period less than 5 years. So far, progression-free survival is good for CAB. Even when both groups are put together, it has been determined that the same survival rate as the one expected for the population of that age group has been obtained. The other study (3) is a comparative trial of LH-RHa + bicalutamide versus LH-RHa + placebo administered for patients with locally advanced or metastatic prostate cancer. The observational period is again short, but in both PSA progression-free survival and time to PSA response, the CAB group was significantly better. Meanwhile, in a successive survey of QOL using FACT-P that was officially translated into Japanese (18), the CAB group showed a significantly better result (19). This is indicative of the perception that the effects of hormone therapy on QOL are different between Japanese and Western patients (20). Therefore, it is important to examine whether or not recent clinical trial results take into account ethnic differences in the broad sense, including the lifestyle and philosophical backgrounds of Japanese and Western people.

In future, in the treatment of prostate cancer in Japan, it is evident that the importance of hormone therapy should be investigated with specific focus on Japanese people. We await the further analysis of the outcome findings, which is the aim of the J-Cap Study.

APPENDIX

J-CaP Home Page: Rules for Use

1. The J-CaP Home Page is to be created as an Internet server.
2. Use of the case database on the J-CaP Home Page is restricted to doctors who are joint researchers and the use of the database requires a user ID and password issued by means of prior registration.
3. Communication between the case database server and users is to be protected by encryption (SSL).
4. The names of institutions and patients (initials) displayed in the case database are to be encoded so that individual patients cannot be identified.
5. Information concerning joint researchers' institutions and patient names (initials) will only be accessible to database administrators with a special ID and password and only at the designated location (administrative secretariat).
6. The ID and password of the above-mentioned administrators will be stored as strictly confidential and no record of them will be kept.
7. The disposal of case data and information concerning joint researcher institutions and patient names (initials) after the completion of the J-CaP Study Group's research period will be determined at a later date by administrators.

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A retrospective study of the treatment of locally advanced prostate cancer by six institutions in eastern and north-eastern Japan

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OBJECTIVE

To investigate patients with locally advanced prostate cancer treated at six academic institutions in eastern and north-eastern Japan from 1988 to 2000, to facilitate the establishment of Japanese guidelines for the diagnosis and treatment of locally advanced prostate cancer.

PATIENTS AND METHODS

The study included 391 eligible patients with locally advanced prostate cancer who were treated by radical prostatectomy (RP), radiotherapy and/or primary hormone therapy. Disease-specific survival rates for these patients were assessed in relation to their clinicopathological characteristics and the types of treatment they received. The Mann–Whitney *U*-test, Kruskal–Wallis, chi-square and log-rank test were used for statistical analysis, as appropriate.

RESULTS

In all, 128 patient with lower prostate-specific antigen levels ($P = 0.023$) and/or better performance status ($P = 0.001$) had RP. Neoadjuvant hormone therapy before RP was the treatment in 68 (53%) of these 128 patients; 66 (52%) received immediate adjuvant hormone therapy. Of 87 patients treated with radiotherapy, 75 (86%) had external beam radiotherapy (EBRT) as the primary treatment with no brachytherapy, and 12 (14%) had brachytherapy as the primary method. Neoadjuvant hormone therapy was given to 56 of the 87 patients (64%); 48 (55%) received immediate adjuvant hormone therapy. Of the 176 patients treated with primary hormone therapy alone, combined androgen blockade and surgical or medical castration was the treatment in 76 (43%) and 85 (48%), respectively. Disease-specific survival rates at 5 years for patients treated with RP, EBRT and primary hormone therapy were 90%, 98%, and 89%, respectively.

CONCLUSION

The treatments provided by the participating institutions did not differ significantly from those set out in European and American guidelines, and short-term disease-specific survival rates for each treatment did not differ significantly from those of historical controls. Further investigation may facilitate the establishment of Japanese guidelines for the diagnosis and treatment of locally advanced prostate cancer.

KEYWORDS

locally advanced prostate cancer, radical prostatectomy, radiotherapy, hormone therapy

INTRODUCTION

The heterogeneity and wide spectrum of locally advanced prostate cancers make it difficult for urologists to determine what constitutes appropriate treatment for individual patients. Radical prostatectomy (RP), radiotherapy and hormone therapy are commonly used alone or combined. Numerous randomized clinical trials [1–9] and unrandomized studies [10–12] have been conducted on each therapeutic approach. Despite the many such clinical trials, the most appropriate therapeutic approach is still under debate in Japan, in terms of survival and quality of life (QoL). Moreover, neither the characteristics of patients with locally advanced prostate cancer nor the types of treatment they receive have been thoroughly investigated in Japan. Because it is necessary to understand these conditions before designing randomized clinical studies or establishing treatment guidelines, we investigated the characteristics of patients in Japan with locally advanced prostate cancer and who were treated at six institutions in eastern and north-eastern Japan from 1988 to 2000, and correlated these with their treatments and outcomes.

PATIENTS AND METHODS

The six Japanese academic institutions participating in this retrospective study were selected from independent institutions in eastern and north-eastern Japan. Patients with locally advanced prostate cancer who were treated at these institutions from 1988 to 2000 with RP, radiotherapy or hormone therapy as the primary method, and who also satisfied several other criteria, were included in the study.

The other criteria consisted of clinical diagnosis and staging in accordance with the TNM system [13], a PSA measurement at initial diagnosis, histopathological diagnosis by systematic TRUS-guided prostate biopsy, and availability of complete treatment records.

Information on 394 patients was compiled from the participating institutions; from this

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TABLE 1 The patients' characteristics by institution and by type of treatment

Variable	Median (range)		Biopsy tumour grade			Performance status		
	Age, years	PSA, ng/mL	Well	Moderate	Poor	0	1	2
Institution								
1	72.0 (58–87)	29.0 (2.0–435)	2	27	11	–	–	–
2	71.0 (57–89)	22.0 (4.7–100)	5	18	10	–	–	–
3	74.0 (51–90)	20.9 (0.6–571)	30	74	33	–	–	–
4	75.0 (55–88)	35.3 (2.3–754)	27	43	14	–	–	–
5	77.5 (64–84)	22.9 (58.3–141)	2	7	3	–	–	–
6	71 (58–92)	37.0 (6.0–538)	11	51	23	–	–	–
Total	73 (51–92)†	27.0 (0.6–754)†	77	220	94*	–	–	–
Type of treatment (n)								
RP (128)	69.0 (51–82)†	22.2 (2.4–434)*	21	77	30	119	9	0
Radiotherapy (87)	70.0 (56–84)	26.6 (2.0–371)	14	50	23	64	22	1
Hormone therapy (176)	78.0 (54–92)	33.7 (0.6–754)	42	93	41	133	41	2

*The Kruskal–Wallis and chi-square test were used to assess the correlation of patient characteristics between institutions; *P < 0.05, †< 0.01, ‡< 0.001.*

information, 391 were deemed to be eligible for the study. The clinicopathological characteristics of the patients, including age at diagnosis, performance status, pretreatment PSA level, and tumour grade, were investigated. Tumour grade was determined using the WHO system in each institution. To facilitate understanding of the patients' background and disease-specific survival (DSS), risk groups were defined by a combination of pretreatment serum PSA level and biopsy tumour grade. Patients with a PSA level of ≤10.0 ng/mL and a well or moderately differentiated tumour were classified as low risk; those with a PSA of 10.1–50 ng/mL and a well or moderately differentiated tumour as intermediate risk; and those with a PSA level of ≥50.1 ng/mL and/or a poorly differentiated tumour as high risk.

The type of treatment, including the application of neoadjuvant and/or adjuvant hormone therapy (N-, AHT) was investigated for the groups treated by RP or radiotherapy. The pathological stage after RP was evaluated according to the TNM system [13]. For the radiotherapy group, the type of radiation therapy, irradiation dose, and use of lymphadenectomy, and for the primary hormone therapy group, the type of hormone therapy, were investigated.

Because criteria for assessing comorbidity and QoL were not standardized across the participating institutions during the 1990s, comorbidity and QoL were not evaluated in this study. The length of follow-up, cause of death and time to death from prostate cancer or other causes were evaluated for each treatment group. Treatment outcome was assessed as DSS rates, using the Kaplan–Meier method, correlated with biopsy tumour grade, PSA level and risk group. The Mann–Whitney *U*-test, Kruskal–Wallis, chi-square and log-rank test were used for statistical analysis, as appropriate, with $P < 0.05$ considered to indicate statistical significance in all tests.

RESULTS

There was a statistically significant difference among institutions in patient age ($P = 0.001$), PSA distribution ($P = 0.011$) and tumour grade ($P = 0.050$), but no significant difference in the distribution of poorly differentiated tumours ($P = 0.564$; Table 1).

RP, radiotherapy and hormone therapy were used as primary treatments for 128, 87 and 176 patients, respectively (Table 2). Younger patients tended to receive a definitive treatment such as RP or radiotherapy as their primary treatment. The participating urologists tended to use RP for patients with lower PSA levels and/or good performance status. The PSA levels were highest in the primary hormone therapy group, lower in the radiotherapy group and lowest in the RP group ($P = 0.023$). There was no significant difference among the three therapeutic approaches in biopsy tumour grade ($P = 0.429$).

RP with no NHT (RP alone) was used in 60 of 128 patients, while NHT preceded RP in 68 (Table 2); NHT was used in those with higher PSA levels ($P = 0.012$). Immediate AHT after RP was used in 66 patients. In the 60 patients treated with RP alone, four of 14 with stage pT3a disease, seven of 12 with stage pT3b and 12 of 19 with stage pN1 received AHT; adjuvant radiotherapy was given to only two of the 12 patients with stage pT3b disease.

Of the 68 patients treated with RP after NHT, immediate AHT was used in 41; 10 of 24 with stage pT2, 10 of 16 with stage pT3a, four of seven with stage pT3b and 17 of 21 with pN1 disease received AHT after RP. Hormone therapy was the most common adjuvant therapy after RP.

In terms of clinical staging, 15 (25%) of the 60 patients treated with RP alone were diagnosed afterward as having stage pT2N0 disease (i.e. their disease was initially overstaged), and 19 (33%) as pN1 (i.e. their disease was initially understaged). Of the 68 patients treated with NHT and RP, despite higher PSA levels, the likelihood of the patient being diagnosed as having stage pT2N0 disease was higher, although this might not promise a longer PSA failure-free survival.

Table 2 also shows the characteristics of the 87 patients treated with radiotherapy. External beam radiotherapy (EBRT) of 70 Gy was used at institution 6, where three-dimensional conformal radiotherapy (3D-CRT) was also used. However, at the other

TABLE 2 The characteristics of patients treated with RP or radiotherapy

Median (range)	RP (128)			EBRT (75)			Brachytherapy (12)	Primary hormone
	RP alone (60)	+NHT (68)	P	Alone (19)	+ NHT (56)	P	+ EBRT (4)*	therapy (176)
Age, years	69.0 (55-79)	69.0 (51-83)	0.817	67.0 (52-82)	68.5 (56-79)	0.579	77.5 (64-84)	78.0 (54-92)
PSA, ng/mL	18.8 (3.6-170)	29.3 (2.4-434)	0.012	34.9 (7.9-337)	25.4 (2.0-371)	0.141	23.0 (8.3-141)	34.8 (0.6-754)
<10	16	12		1	12		3	29
10-50	36	39		12	28		6	83
>50	8	17	0.179	6	16	0.267	3	64
Biopsy tumour grade			0.319					
Well	11	10		3	9		2	42
Moderate	32	45		12	31		7	93
Poor	17	13		4	16	0.798	3	41
Risk group			0.704					
Low	19	17		0	9		2	21
Intermediate	20	25		10	21		4	70
High	21	26		9	26	0.147	6	85
Pathological stage			0.393					
pT2	15	24						
pT3	26	23						
pN1	19	21						
Lymph node dissection (20)								
pN0				0	17		0	
pN1				0	3		0	
Dose, Gy				60 (60-70)	66 (50-72)			
Method								
Standard EBRT				18	25		4	
3D-CRT				1	16		0	
Heavy particle RT				0	15		0	
NHT								
duration, months		4.8 (0.5-30)			4.0 (1-4)			
Method								
CAB		41			27			76
Castration including medical castration		16			20			85
Anti-androgen monotherapy		5			1			7
Oestrogen		7			8			8
Adjuvant therapy:								
+ hormone	23	41		8	40		0	
no hormone				11	16		12	
+ radiation	2	0						
no radiation	35	27						

The Mann-Whitney U-test and chi-square test were used to evaluate the correlation of characteristics between treatment groups. This group was too small to calculate P values and includes all 12 patients. CAB, combined androgen blockade; RT, radiotherapy.

institutions radiation doses were generally lower. NHT was used in 56 of the 75 patients treated with EBRT with no brachytherapy, and AHT in 40 of the 56 and eight of the 19 who were treated with EBRT combined with NHT and EBRT alone, respectively. Therefore, some hormone therapies were concomitant in 64 of the 75 patients treated with EBRT with no brachytherapy (85%). Twenty of the 75 patients treated with EBRT and no brachytherapy had a lymphadenectomy; only 12 men received brachytherapy as primary therapy.

The characteristics of the 176 patients treated with primary hormone therapy are also shown in Table 2; for most of these patients, combined androgen blockade and medical/surgical castration were selected as the primary hormone therapy.

For treatment outcome, the median (range) follow-up for all eligible patients was 37 (1–137) months. The DSS rate was independently calculated for each treatment group. Of the RP group, 13 of the 128 patients died from prostate cancer; the DSS rates at 5 and 10 years for these patients were 90% and 49.5%, respectively (Fig. 1a–d). Patients with higher tumour grades tended to have the poorest DSS rates ($P = 0.316$; Fig. 1a). The P