Background factors and short-term health-related quality of life in patients who initially underwent radical prostatectomy or androgen deprivation therapy for localized prostate cancer in a Japanese prospective observational study (J-CaP Innovative Study-1)

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Abstract
Background: This prospective observational study elucidated the usefulness of hormonal therapy for localized prostate cancer. Background factors and the health-related quality of life in patients who initially underwent radical prostatectomy (RP) or primary androgen deprivation therapy (PADT) for localized prostate cancer are summarized.

Materials and methods: Patients aged 67–76 years with clinical stage T1c or T2 localized prostate cancer treated with PADT or RP, a prostate-specific antigen concentration of <20 ng/mL, and Gleason score of ≤7 were included. Health-related quality of life results estimated by the Medical Outcomes Study 8-Item Short-Form Health Survey (SF-8) and the Expanded Prostate Cancer Index Composite (EPIC) were investigated.

Results: In total, 850 patients who underwent RP and 370 patients who underwent PADT were enrolled. The proportion of patients with comorbidities of hypertension, cardiovascular disease, and/or cerebrovascular disease was greater in the PADT group than in the RP group. The proportion of patients deciding on treatment was significantly higher in the PADT group than in the RP group. In the RP group, the scores of many SF-8 and EPIC domains decreased at 3 months following surgery and returned to baseline levels at 1 year. In the PADT group, several domains gradually decreased during the year after treatment initiation. The proportion of patients with decreased satisfaction scores at 1 year compared with baseline was lower in the PADT group than that in the RP group.

Conclusion: Treatment risk influenced decisions on primary treatment for localized prostate cancer. Although there was a selection bias, short-term overall satisfaction in the PADT group was superior to that in the RP group in this clinical study.

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1. Introduction

Androgen deprivation therapy (ADT) has become the standard method for managing advanced prostate cancer since it was first reported >60 years ago by Huggins and Hodges. It remains the first choice of treatment for advanced prostate cancer and is frequently used as neoadjuvant or adjuvant therapy for patients undergoing radical prostatectomy (RP) or radiotherapy (RT). Furthermore, ADT may be used as a primary treatment for localized prostate cancer, particularly in elderly patients. Recent analyses of the patterns of clinical practice revealed that many patients with localized cancer who are conservatively treated receive primary ADT (PADT) rather than local treatment or active surveillance/watchful...
The European Urological Association guidelines for prostate cancer recommend PADT as the treatment of choice for metastatic disease for older men with locally advanced tumors and for those who are unsuitable for radical therapy.\(^5\)\(^-\)\(^8\)

Several studies have reported the efficacy of ADT for localized prostate cancer based on experiences in Japan.\(^5\)\(^-\)\(^8\) Of these, Akaza et al\(^a\) demonstrated that the overall survival rate of patients with localized or locally advanced prostate cancer treated with PADT was equivalent to the life expectancy of healthy age-matched subjects. Additionally, Egawa et al reported that hormonal therapy was as effective as RP for the disease-specific survival of patients with well-differentiated prostate cancer.\(^8\) Moreover, a retrospective multicenter study reported the efficacy of hormonal therapy in Japanese patients with localized or locally advanced prostate cancer.\(^9\) These findings indicated that some patients with localized prostate cancer might be fit for PADT, although there are no criteria for optimal patient selection due to the lack of comparative studies between PADT and other treatments for localized prostate cancer.

To address this issue, we initiated a clinical study, the Japan Study Group of Prostate Cancer (J-CaP) Innovative Study-1. This observational, non-randomized, prospective comparative study is the first to compare PADT and RP for localized prostate cancer. We also summarized the background factors and short-term health-related quality of life (HRQoL) of patients enrolled in the J-CaP Innovative Study-1. In this paper, we present preliminary results from the clinical study and describe the study protocol.

2. Materials and methods

The patient cohort in this multicenter, prospective observational study to compare the clinical outcomes of RP versus PADT for localized prostate cancer was limited to patients aged 67–76 years, with stage T1c or T2N0M0 prostate cancer, prostate-specific antigen (PSA) concentrations <20 ng/mL, and Gleason score (GS) ≤7. For each patient, urologists in the participating institutions presented optional treatments, which included RP, RT, or PADT. Patients who selected RP and PADT were enrolled in this study.

Clinical staging was determined in accordance with the unified TNM criteria based on the results of a digital rectal examination, transrectal ultrasonography, computed tomography, magnetic resonance imaging, and bone scintigraphy.\(^9\)\(^,\)\(^10\) Pathological findings were evaluated based on the 2005 International Society of Urological Pathology GS criteria\(^11\) by pathologists in each institution. For patients who underwent RP, urologists in the participating institutions chose the surgical procedures, which included retroperitoneal, perineal, laparoscopic, and robot-assisted prostatectomy. PADT consisted of bicalutamide (Casodex, 80 mg orally once a day; AstraZeneca, Cambridge, England) plus leuprorelin acetate (Luprin; Takeda Chemical Industries, Osaka, Japan) at 3.75 mg or 11.25 mg by subcutaneous injection every 4 weeks or 12 weeks.\(^12\) Of the 1,240 patients initially registered from January 2007 to October 2011, 20 were excluded (7 withdrew consent, 4 had serum PSA >20 ng/mL, 4 had GS >8, and 2 received PADT with a different antiandrogen). Therefore, 850 patients who underwent RP and 370 patients who received PADT were enrolled in this study. A written consent to participate was obtained from all patients, and all examinations were performed under the approval of the institutional review board of each medical institution (UMIN 00000570).

In this prospective observational study, the primary endpoint was overall survival, and secondary endpoints were as follows: (1) disease-specific survival; (2) progression-free survival; and (3) HRQoL. Serum PSA level was assessed at follow-up examinations conducted every 4–12 weeks after RP or at the beginning of PADT. Disease progression was defined as an increase in PSA and/or recurrent findings on imaging studies (i.e., computed tomography, magnetic resonance imaging, or bone scintigraphy). To comprehensively evaluate physical and psychosocial well-being, two validated HRQoL questionnaires, the Medical Outcomes Study 8-Item Short-Form Health Survey (SF-8) and the Expanded Prostate Cancer Index Composite (EPIC), were administered before treatment and at 3-month and 12-month follow-ups. The SF-8 is an eight-item, multipurpose survey that evaluates the physical and mental health of patients using eight multi-item scales to assess the physical function, limitations due to health problems, bodily pain, general health perception, vitality, social function, limitations due to emotional problems, and mental health.\(^13\) Furthermore, scores for physical and mental health components were calculated based on the survey findings. Disease-specific QoL was examined using the EPIC, which comprised 50 items regarding function and discomfort in the urinary, bowel, sexual, and hormonal domains, consisting of five (sexual function, discomfort, irritation/obstruction, incontinence, and summary), three (bowel function, discomfort, and summary), three (sexual function, discomfort, and summary), and three (hormonal function, discomfort, and summary) scales, respectively.\(^14\) For both the questionnaires, scores ranged from 0 to 100, with higher scores indicating better health status.

The characteristics and background factors of patients in the RP and PADT groups were compared using the Mann–Whitney U test or Fisher’s exact test. Almost all SF-8 and EPIC scores for HRQoL were relatively high and did not follow a Gaussian distribution. Because comparative statistical analysis might not be appropriate, curves for each HRQoL score were constructed. All statistical analyses were performed using commercially available software, i.e., SPSS Statistics (IBM Corp., Armonk, NY, USA) and Prism (GraphPad Software, San Diego, CA, USA). For all analyses, a probability (P) value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics and background

Baseline patient characteristics are shown in Table 1. The median patient age was significantly greater in the PADT group than in the RP group. Median age at diagnosis was 71 (67–76) years in the RP group and 73 (67–76) years in the PADT group (P <0.001). Median cT stage was T2b in 55 (6.5%) patients in the RP group and 21 (5.7%) patients in the PADT group (P <0.001). Median initial PSA was 7.57 (9.0–19.9) ng/mL in the RP group and 8.53 (12.6–19.9) ng/mL in the PADT group (P <0.001).

| Variables                  | Type of treatment | n (%) | P       |
|----------------------------|-------------------|-------|---------|
| No. of patients            |                   | 850   | 370     |         |
| Age at diagnosis (y)       |                   |       |         |         |
| Median (range)             |                   | 71    | 73 (67–76) | <0.001 |
| Performance status         |                   |       |         |         |
| 0                          |                   | 624   | 628 (90.8) | <0.001 |
| 1                          |                   | 22    | 26 (7.0)   |         |
| 2                          |                   | 0     | 3 (0.8)    |         |
| Unknown                    |                   | 3     | 5 (1.4)    |         |
| Initial PSA, ng/mL         |                   | 7.57  | 8.53 (12.6–19.9) | <0.001 |
| Gleason score              |                   |       |         |         |
| ≤6                         |                   | 422   | 193 (52.2) | 0.394  |
| 7                          |                   | 428   | 176 (47.8) |         |
| CT stage                   |                   |       |         |         |
| T1c                        |                   | 547   | 249 (67.3) | ≤T2a vs. T2b |
| T2a                        |                   | 205   | 59 (15.9)  | 0.013   |
| T2b                        |                   | 55    | 21 (5.7)   | ≤T2b vs. T2c |
| T2c                        |                   | 43    | 41 (11.1)  | <0.001  |

RP, primary androgen deprivation therapy; PSA, prostate-specific antigen; RP, radical prostatectomy.

Mann–Whitney U test.

Fisher’s exact test.
the RP group (71.0 years vs. 73.0 years, respectively). More than 90% of patients in both groups had a good performance status (0). However, the proportion of patients with a performance status of 1 or 2 was significantly higher in the PADT group than in the RP group. The median PSA level at diagnosis was significantly lower in the RP group than in the PADT group (7.57 ng/mL vs. 8.53 ng/mL, respectively). Approximately half of all patients had a GS <7, and there was no statistically significant difference in the proportions between groups. In both groups, the proportion of stage T1c patients was high. However, the proportion of those with T2b and T2c was significantly higher in the PADT group than in the RP group.

Treatment decisions made by urologists at the participating institutions were surveyed using a questionnaire. In both groups, the patient’s ability to select the treatment was a major factor. However, the proportion of patients deciding on the treatment was significantly higher in the PADT group than in the RP group (Table 2).

Treatment decisions made by urologists at the participating institutions were surveyed using a questionnaire. In both groups, the patient’s ability to select the treatment was a major factor. However, the proportion of patients deciding on the treatment was significantly higher in the PADT group than in the RP group (Table 2). When participating institutions were asked about the reason for treatment decisions, the responses of patient age were higher in the RP group and comorbidities were higher in the PADT group (Table 3).

Of the patients who underwent RP, approximately 90% were performed via a retropubic approach. Lymph node dissection was performed in 87.1% of all patients, and nerve-sparing radical retropubic prostatectomy was performed in 31.9% patients (Table 4).

### HRQoL

The completion rates for SF-8 and EPIC questionnaires before treatment were 95.1% and 94.7%, respectively. The completion rates for SF-8 and EPIC were 88.8% and 88.7%, respectively, at the 3-month follow-up and 76.4% and 74.9%, respectively, at the 12-month follow-up.

The SF-8 questionnaire contains eight scales used to generate summary scores for the physical and mental components. In the RP group, the scores for each domain, except for mental health, decreased at 3 months following surgery and returned to baseline levels at 1 year (Fig. 1A).

In the PADT group, the scores gradually decreased in several domains, including physical function, whereas the mental health scores increased 1 year after the start of treatment (Fig. 1C). The physical and mental component summary scores for the RP and PADT groups are shown in Fig. 1B and D, respectively.

The mean EPIC QoL scores over time for each group are shown in Fig. 2A and B. The mean urinary function score of the RP group decreased at 3 months after treatment and improved at 12 months (Fig. 2A). The mean bowel and hormonal scores of the RP group did not change at 1 year after RP (Fig. 2A). In the PADT group, there were no changes in the urinary and bowel scores at 1 year after the initiation of PADT (Fig. 2B). The hormonal score from the EPIC questionnaire, which included hot flashes and breast tenderness, gradually decreased over time in the PADT group (Fig. 2B). The mean sexual scores for both groups were low at baseline, decreased at 3 months after treatment, and did not return to baseline (Fig. 2A and B). There were no statistically significant differences in urinary and sexual QoL scores between RP patients receiving nerve-sparing or non-nerve-sparing procedures (data not shown).

The overall treatment satisfaction scores from the EPIC questionnaire for each group are shown in Fig. 2C and D. The mean score of the RP group did not change during the study period (Fig. 2C). In contrast, scores in the PADT group increased slightly 1 year after the start of treatment (Fig. 2D). Significantly more patients in the RP group than in the PADT groups reported a lower satisfaction score at 1 year compared with baseline [250 (29.3%) vs. and 82 (22.1%), respectively, \( P = 0.0089 \); Fisher’s exact test].

### 4. Discussion

Standard treatment for localized prostate cancer traditionally involves RP and RT. However, in actual clinical practice, many patients with localized cancer who are conservatively treated receive PADT rather than local treatment or active surveillance/watchful waiting. This tendency may reflect the physician’s experience that PADT is effective for localized prostate cancer. Accordingly, several studies have revealed the clinical efficacy of PADT for localized prostate cancer, especially in the Japanese population. The most recent study using data from the J-CaP registry...
and CaPSURE revealed that both cancer-specific and overall survival were substantially better for patients treated in Japan than for those treated in the United States, even after adjusting for disease risk, patient characteristics, and the type of ADT.\textsuperscript{18} Experiences with PADT in Japan resulted in the National Comprehensive Cancer Network Asia Consensus Statement in which PADT was endorsed as an acceptable alternative for most patients with prostate cancer, except for those at a very low risk for the disease.\textsuperscript{19} To investigate the efficacy and adverse effects of PADT for localized prostate cancer, the J-CaP IS-1 study was initiated. This observational, prospective, comparative clinical study includes patients aged 67–76 years with localized clinical stage T1c or T2 prostate cancer, a PSA of <20 ng/mL, and GS of ≤7 who were treated with RP or PADT alone. The results of the J-CaP IS-1 should clarify the efficacy and optimal indications of PADT for localized prostate cancer.

The aim of the present study was to summarize the background factors and HRQoL of patients enrolled in the J-CaP Innovative Study-1. In terms of baseline patient characteristics, all the enrolled

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**Fig. 1.** Mean scores of each domain in the Medical Outcomes Study 8-Item Short-Form Health Survey (SF-8) for patients treated with (A) radical prostatectomy and (C) primary androgen deprivation therapy. Mean physical and mental component summary scores in patients treated with (B) radical prostatectomy and (D) primary androgen deprivation therapy.

**Fig. 2.** Mean scores of each domain in the EPIC for patients treated with (A) radical prostatectomy and (B) primary androgen deprivation therapy. Mean scores for overall satisfaction in the Expanded Prostate Cancer Index Composite (EPIC) of patients treated with (C) radical prostatectomy and (D) primary androgen deprivation therapy.
patients were at a low or intermediate risk of localized prostate cancer. However, those in the PADT group were at a greater risk of disease than those in the RP group (Table 1). Moreover, the proportion of patients with comorbidities of hypertension, cardiovascular disease, and/or cerebrovascular disease was greater in the PADT group than in the RP group. Although closer analysis using the comorbidity index could not be performed in this study, it is interesting that the stage of disease, patient age, and comorbidities influenced the decision of primary treatment of localized prostate cancer in this clinical study.

Several studies, including our previous study, have described HRQoL among Japanese men treated for localized prostate cancer.20–23 Although it is difficult to compare HRQoL among different treatment modalities, it is notable that Japanese patients with localized prostate cancer were more likely than American men to report poor sexual desire and function at baseline, which was consistent with the results of this study.24 The differences in sexual QoL scores between RP patients receiving nerve-sparing or non-nerve-sparing procedures did not significantly support this finding. A recent review of several studies regarding prostate cancer survivorship found that prostate cancer survivors of different races might have different outcomes and needs concerning cancer control, expectations, general, urinary, bowel, and sexual QoL.24 Because the overall satisfaction of patients in this study treated with PADT was superior to those treated with RP, it is possible that decreased physical and sexual functions were not important issues for the patients during the 1-year treatment period. The treatment decision, which patients made themselves, and the expectations of treatment may be more important for Japanese men treated for prostate cancer.

There were several limitations to this observational, non-randomized, clinical study. First, selection bias of patients in both groups could not be avoided. In a recent Japanese surveillance study of prostate cancer, 6–8% and 14–19% of patients aged 65–69 years and 70–74 years, respectively, with low or intermediate localized prostate cancer received ADT.25 In this clinical study, the proportion of enrolled patients who received PADT was higher than those in this surveillance study. Therefore, these results might not reflect actual clinical practice, especially in the RP group. Second, HRQoL scores from SF-8 and EPIC questionnaires could not be statistically evaluated in both groups. Nonetheless, these data reveal trends in HRQoL and overall satisfaction in both groups. Third, this report includes preliminary data on results from the first year after treatment started. HRQoL in the RP group, especially related to urinary incontinence and sexual function, may recover after 1 year of RP. The primary endpoint of overall survival for patients treated with RP and PADT will be reported in the future.

However, in this preliminary study, we demonstrated the short-term satisfaction of patients treated with ADT. Although the final results of this clinical study, including overall survival, efficacy, and the adverse effect of treatments are pending, this unique observational, prospective clinical study is expected to offer novel insight regarding the treatment options for localized prostate cancer.

Conflicts of interest

None declared.

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