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Health utility and health-related quality of life of Japanese prostate cancer patients according to progression status measured using EQ-5D-5L and FACT-P

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Abstract

Purpose To obtain health utility data to allow for cost-effectiveness analysis in groups stratified by disease progression along with health-related quality of life (HRQoL) information in Japanese prostate cancer (PC) patients.

Methods In this cross-sectional observational study, EuroQol-5 Dimension- 5 Level (EQ-5D-5L), EuroQol Visual Analog Scale (EQ-VAS), and Functional Assessment of Cancer Therapy-Prostate (FACT-P) measures were used to examine utility, VAS scores, and disease-specific HRQoL, respectively. Scores obtained were statistically examined for the correlation among measures and domains. Parameter estimates of statistically significant factors were assessed using generalized linear models (GLM).

Results A total of 380 patients stratified by their disease progression status were analyzed. The numbers (%) of patients in groups stratified as having localized (L), localized progression (LP), distant metastatic (DM), and DM-castration-resistant PC (CRPC) were 275 (72.4), 40 (10.5), 27 (7.1), and 38 (10.0), respectively. EQ-5D-5L mean (standard deviation, SD) scores of L, LP, DM, and DM-CRPC in study participants were 0.87 (0.15), 0.86 (0.15), 0.85 (0.18), and 0.84 (0.17), respectively. The mean (SD) scores assessed by EQ-5D-5L, EQ-VAS, and FACT-P instruments were 0.86 (0.16), 74.6 (16.8), and 110.8 (19.6), respectively. Utility scores correlated well with FACT-P scores. Eastern Cooperative Oncology Group performance status had significant influences on all instruments' scores.

Conclusions We obtained health utility and HRQoL scores of Japanese PC patients stratified by disease progression in detail. Our results will be useful for establishing cost-effectiveness analyses in Japanese PC settings.

Keywords Health-related quality of life (HRQoL) · EQ-5D-5L · EQ-VAS · FACT-P · Prostate cancer

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Introduction

In Japan, the number of patients with prostate cancer (PC) has rapidly increased over several decades according to ageing and dietary changes. Recently, novel PC treatments were developed in accordance with the new understanding of PC pathology [1, 2]. Simultaneously, clinical experience with new hormone treatments and anticancer drugs has continued to increase. Moreover, new radiotherapy (external and interstitial) devices have also been developed. These changes might contribute to the longer survival outcomes and safety of active surveillance for PC. However, these development and modification of PC treatment allow for increases in therapeutic strategy options [2].

In these contexts, the evidence-based clinical practice guideline for PC 2016 (3rd ed.) was developed for 5

purposes. Of these, we primarily focused on the guideline "to do away with ineffective therapies, and thereby alleviate both human and economic burdens" while the authors of this guideline are "confident that this guideline will help in the decision-making related to the treatment of PC" [2]. As background to this guideline, newly developed and high-priced health care technologies are exacerbating the cost-burden on the Japanese government [3]. Therefore, there is an urgent need to introduce health-economic evaluation in Japan. For this evaluation, the accumulation of data of utility scores are necessary.

In recent years, cost-effectiveness evaluation in Japan was implemented on a trial basis, and the guideline for the economic evaluation in Japan was officially approved only recently, in 2016 [4]. In contrast, while treatment methods have developed, the evaluation of health-related quality of life (HRQoL) in Japan is scarce, and scientists committed to this economic evaluation guideline [4] state that they, as Japanese health economists must promote the collection of preference-based QoL (health utility) and cost data [4]. Indeed, not only non-preference-based but also preference-based QoL data for Japanese PC patients are also insufficient [5–7]. Health utility measures are used for cost-effectiveness analysis, as a means to use outcome for quality-adjusted life years (QALY) [8, 9]. Health utility scales have a score of 0 (dead) to 1 (perfect health), though it allows for less than 0 (negative) states indicating worse than death depending on the specific instruments used [9]. Utility scores are used as quality weights in QALY calculations [8, 9]. Former studies that measured Japanese health utility did not stratify data based on disease progression status [5, 7, 10]. To perform cost-effectiveness analysis, it is important to evaluate HRQoL stratified by PC progression state in order to apply utilities to state transition models [11, 12].

One of the most frequently used health economic models in cost-effectiveness analysis is a multistate Markov model. These models consist of states chosen to represent clinically and economically important events [12]. As an example of the most simplified model, Collins et al. constructed 2-state (dead and alive) Markov model for analysis of docetaxel [13]. In recent cost-effectiveness studies of prostate cancer, the relatively simplified Markov models used consist of four or five statuses (including status of death), compare prostate cryotherapy versus androgen deprivation therapy for radiation recurrent PC, radium-223 versus abiraterone and enzalutamide for castration-resistant PC (CRPC) patients, and localized (L) PC [11, 14, 15]. Models with more than 7 states were used to evaluate cost-effectiveness of active surveillance, brachytherapy for L PC, and recurrent PC [11, 16, 17]. The statuses used to construct models should reflect the natural history of disease and results of intervention. The international society of Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision Making (MDM) published a report about best practice for a state transition model (Markov and micro simulation model) [18]. This report recommends that the model states "should adequately capture the types of intervention as well as the intervention's benefit and harms" [18]. To follow this recommendation, we need to accumulate clinical data including preference-based generic HRQoL.

This study measured preference-based generic HRQoL, that is health utility, using the EuroQol-5 Dimension-5 Level (EQ-5D-5L). In addition, quantitative self-imaginable health outcomes using EQ visual analog scale (EQ-VAS) belonging to the EQ-5D-5L questionnaire and non-preference-based disease-specific HRQoL using Functional Assessment of Cancer Therapy-Prostate (FACT-P) were measured in Japanese PC patients. The scores obtained were analyzed according to the patients' disease progression status. In addition, we investigated the correlation among instruments and possible factors affecting these scores.

Methods

Study design and data collection

We conducted a cross-sectional observational study recruiting PC patients from 5 hospitals in Japan between February and December 2017. All hospitals were university hospitals and cover wide regions of Japan from Kanto (including Tokyo) to the Shikoku region. In each hospital, patients selected were ≥ 20 years of age and pathologically diagnosed with PC. This study was conducted in agreement with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Ritsumeikan University (BKC-2016-042) and each participating hospital. Informed consent was obtained from all patients included in this study. When the number of patients who registered in this study reached 100, patient recruitment in each hospital was completed. We explained to patients that this study involved only voluntary cooperation that there was no obligation or disadvantage regarding the decision to cooperate, and that they could withdraw consent or drop out at any time during our investigation. Patients who participated in this study were asked to complete a self-administered questionnaire. The completed questionnaires were put into an envelope and posted to the data center by the patients themselves, without being seen by their doctors. Simultaneously, their doctors completed questionnaires, which are asked for patient's medical information, such as progression of cancer.

Questionnaires

Patients responded to items on socio-demographic, EQ-5D-5L, EQ-VAS, and FACT-P questionnaires. The

socio-demographic questions consisted of birth date, family members (e.g., With whom do you live?), education level (e.g., What is your highest academic background?), job (e.g., What is your job? Did you change your job after suffering from PC?), income (e.g., If you do not mind, please tell us about your household income), and other diseases (e.g., Do you have disease(s) other than PC?). These questionnaires were mostly offered in multiple-choice formats.

The EQ-5D is an instrument that measures preference-based general health status and provides utility scores [9]. This instrument is one of the most widely used in health economic analysis [4, 19–23]. The maximum score of 1 represents full health and the minimum score of 0 represents death. It is a 5-dimensional utility instrument consisting of domains about morbidity, self-care, usual activities, pain or discomfort, and anxiety or depression. The EQ-5D-5L version was used in this study. Each domain is divided into 5 levels of severity (none, slight, moderate, severe, extreme problems, or unable to). The change from the earlier version of EQ-5D-3 Level (3L) to the 5L improved its sensitivity and decreased the incidence of a minus utility score "worse than dead" [21, 23]. Self-rated answers by each patient were presented as a 5-digit number code where each number reflects the severity level of the individual dimensions. For example, code "11111" represents full health. Each number code represents a unique health state and there are 3125 ($=5^5$) health statuses that can be evaluated. To convert each code to EQ-5D-5L utility scores, we used the Japanese tariff [23] provided by the EuroQol group. For the EQ-VAS, patients evaluated their self-perceived health state with endpoints representing the best (100) and worst (0) health, and marked it on a 100-point vertical scale [19, 24, 25].

The Japanese FACT-P (version 4) questionnaires asked patients a total of 39 questions with a 5-point response scale ranging from "not at all" to "very much". These answers were scored in accordance with the instructions provided by the Functional Assessment of Chronic Illness Therapy (FACIT), as found on www.facit.org. The questionnaire consisted of 5 domains, including physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and PC subscale (PCS). The FACT-P total score is obtained by adding these 5 domain scores. The maximum scores of PWB, SWB, EWB, FWB, PCS, and FACT-P total score are 28, 28, 24, 28, 48, and 156, respectively [26].

Medical information

The medical information of the patients who participated was provided by their physicians in charge after informed consent was given; the filled-out questionnaires were sent by mail and returned by patients to the data center. Briefly, the presence or absence of cancer progression, prostate-specific antigen (PSA) concentration [2, 26, 27], number of days from the last treatment, presence or absence of other diseases, Eastern Cooperative Oncology Group (ECOG) performance status (PS) [28–30], and Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [31] were collected by the report form.

Statistical analysis

Socio-demographic characteristics, medical information, and mean health utility and HRQoL scores and standard deviation (SD) were summarized by 4 cancer progression groups: L, localized progressive (LP), distant metastatic (DM), and DM-CRPC patients. Steel tests were performed to confirm differences in each score between individual cancer progression groups.

To clarify the degree of overlap between the instruments, Spearman's rank correlation coefficients were calculated not only among each instrument, but also among FACT-P domains.

The possible determinants for health scores in socio-demographic and medical factors described above were explored using step-wise method. EQ-5D-5L, FACT-P, and EQ-VAS scores served as dependent variables. The analyses were performed by including only statistically significant variables by step-wise methods, followed by generalized linear model (GLM). Family and link functions used were determined by reference to Akaike's Information Criterion (AIC) values and residuals. We calculated estimate values to determine the effect and direction of socio-demographic variables. Registered hospitals were set as dummy variables in the models.

The level of statistical significance was set at 5% ($p < 0.05$). JMP Pro 14.1.0 (SAS Institute Inc. Cary, NC, USA) and R version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria) were used for our analyses.

Results

Patient characteristics

For this study, 100 patients were registered at each hospital ($n = 500$ in total), informed consent was obtained from 493 of these patients, and answered questionnaires were returned from 453 patients. Of these, we could not obtain scores due to missing answers in EQ-5D-5L and/or FACT-P scoring questionnaire(s) ($n = 69$). Furthermore, 4 patients could not be stratified into a cancer progression group due to missing information in their physician report. As a result, data from 380 patients (76.0%) were analyzed. The socio-demographic and medical information collected are shown in Table 1. The number (%) of patients in the L, LP, DM, and DM-CRPC

Table 1 Socio-demographic and clinical characteristics of patients stratified by prostate cancer progression group, *n* (%)

	L *n* = 275	LP *n* = 40	DM *n* = 27	DM- CRPC n = 38	Total *n* = 380
Age (mean ± SD years)	73.2 ± 7.5	73.0 ± 8.2	73.7 ± 9.3	73.7 ± 7.3	73.3 ± 7.7
Highest education[a]					
Junior school or less	53 (19.3)	7 (18.9)	8 (32.0)	13 (35.1)	81 (21.7)
High school	100 (36.5)	14 (37.8)	9 (36.0)	12 (32.4)	135 (36.2)
College or more	121 (44.2)	16 (43.2)	8 (32.0)	12 (32.4)	157 (42.1)
Income[a,b]					
≦¥3,000,000/year	87 (33.1)	16 (44.4)	8 (33.3)	12 (33.3)	123 (34.3)
> ¥3,000,000/year–≦¥5,000,000/year	111 (42.2)	12 (33.3)	10 (41.7)	11 (30.6)	144 (40.1)
> ¥5,000,000/year	65 (24.7)	8 (22.2)	6 (25.0)	13 (36.1)	92 (25.6)
Job changes[c]	89 (37.1)	12 (31.6)	7 (28.0)	19 (61.3)	127 (38.0)
Living with[a]					
Wife	150 (54.5)	24 (61.5)	14 (56.0)	19 (50.0)	207(54.9)
Wife and other family member(s)	90 (32.7)	13 (33.3)	6 (24.0)	16 (42.1)	125 (33.2)
Alone	22 (8.0)	2 (5.1)	5 (20.0)	0 (0.0)	29 (7.7)
Other	13 (4.7)	0 (0.0)	0 (0.0)	3 (7.9)	16 (4.2)
Health status					
PSA concentration (mean ± SD ng/mL)	2.2 ± 14.3	1.9 ± 6.3	17.3 ± 56.5	60.6 ± 140.3	9.0 ± 50.6
Days from the last treatment (mean ± SD days)	6.8 ± 20.6	7.3 ± 19.9	0	0	5.7 ± 18.8
Suffering other disease(s)[d]	269 (97.8)	39 (97.5)	24 (88.9)	37 (97.4)	369 (97.1)
ECOG performance status[a]					
0	240 (91.3)	35 (87.5)	20 (76.9)	22 (59.5)	317 (86.6)
1	22 (8.4)	5 (12.5)	5 (19.2)	10 (27.0)	42 (11.5)
≧2	1 (0.4)	0 (0.0)	1 (3.8)	5 (13.5)	7 (1.9)
Maximal CTCAE grade[a]					
0	142 (51.6)	16 (40.0)	23 (85.2)	14 (36.8)	195 (51.3)
1	74 (26.9)	11 (27.5)	3 (11.1)	7 (18.4)	95 (25.0)
≧2	59 (21.5)	13 (32.5)	1 (3.7)	17 (44.7)	90 (23.7)
Registered hospital[a]					
Hospital A	53 (19.3)	7 (17.5)	1 (3.7)	16 (42.1)	77 (20.3)
Hospital B	60 (21.8)	6 (15.0)	6 (22.2)	8 (21.1)	80 (21.1)
Hospital C	49 (17.8)	4 (10.0)	9 (33.3)	3 (7.9)	65 (17.1)
Hospital D	54 (19.6)	22 (55.0)	3 (11.1)	5 (13.2)	84 (22.1)
Hospital E	59 (21.5)	1 (2.5)	8 (29.6)	6 (15.8)	74 (19.5)

[a]Does not total 100 due to rounding

[b]Exchange rate was 1 USD = 112 JPY in October 2018

[c]Patients who changed their job following cancer diagnosis

[d]Includes hypertension, diabetes, hyperlipidemia, other cancer and prostatic hypertrophy

L localized, *LP* localized progressive, *DM* distant metastatic, *DM-CRPC* distant metastatic castrate-resistant prostate cancer, *SD* standard deviation, *PSA* prostate-specific antigen [2, 26, 27], *ECOG* Eastern Cooperative Oncology Group [28], *CTCAE* common terminology criteria for adverse events [30]

Total number of patients (*n*) = 380

cancer progression groups were 275 (72.4), 40 (10.5), 27 (7.1), and 38 (10.0), respectively.

Health utility, HRQoL, and VAS scores

Health utility, HRQoL, and VAS scores according to cancer progression groups are presented in Table 2. EQ-5D-5L mean (SD) scores, which can be used for cost-effectiveness analysis, of L, LP, DM, and DM-CRPC patients were 0.87 (0.15), 0.86 (0.15), 0.85 (0.18), and 0.84 (0.17), respectively. The total mean (SD) EQ-5D-5L, EQ-VAS, and FACT-P scores were 0.86 (0.16), 74.6 (16.8), and 110.8 (19.6), respectively. Distributions of these scores were presented in histograms (Fig. 1). Strong ceiling effects [32]

Table 2 Health utility and HRQoL scores according to cancer progression groups, mean ± SD

	L $n=275$	LP $n=40$	DM $n=27$	DM-CRPC $n=38$	Total $n=380$	L versus LP $p^{\dagger}$	L versus DM $p^{\dagger}$	L ersu DM-CRPC $p^{\dagger}$
EQ-5D-5L	0.87 ± 0.15	0.86 ± 0.15	0.85 ± 0.18	0.84 ± 0.17	0.86 ± 0.16	–	–	–
EQ-VAS	74.9 ± 15.7	79.6 ± 13.2	76.2 ± 21.8	66.3 ± 20.6	74.6 ± 16.8	–	–	*
FACT-P	112.1 ± 19.5	106.5 ± 19.3	111.8 ± 23.5	105.0 ± 16.4	110.8 ± 19.6	–	–	–
Physical wellbeing	25.0 ± 3.9	24.9 ± 3.0	24.4 ± 4.4	22.5 ± 4.3	24.7 ± 3.9	–	–	**
Social wellbeing	14.8 ± 7.6	10.8 ± 6.4	15.3 ± 8.5	15.7 ± 5.2	14.5 ± 7.4	*	–	–
Emotional wellbeing	19.6 ± 3.7	19.9 ± 4.7	18.8 ± 4.7	17.0 ± 3.8	19.3 ± 4.0	–	–	**
Functional wellbeing	19.2 ± 7.2	17.0 ± 7.7	20.4 ± 6.7	18.3 ± 5.4	19.0 ± 7.1	–	–	–
PCS	33.5 ± 7.0	34.0 ± 6.7	32.9 ± 8.6	31.4 ± 5.5	33.3 ± 7.0	–	–	–

L localized, *LP* localized progressive, *DM* distant metastatic, *DM-CRPC* distant metastatic castrate-resistant prostate cancer, *PCS* prostate cancer subscale score

Statistically significant differences between stages as a reference stage L were examined using the †steel test labeled with $^{*}p<0.05$ and $^{**}p<0.001$

were observed in the EQ-D-5L score. Among all three instruments, the group of DM-CRPC patients showed the lowest scores (Table 2). Statistical significance between groups, using reference stage L, examined using the steel test were detected in EQ-VAS and 3 FACT-P domains (PWB, EWB, and SWB). The EQ-VAS, PWB, and EWB showed that the scores of the DM-CRPC group were significantly different from the reference score L (Table 2). In contrast, SWB showed that the LP cancer group had a statistically significant lower scores than L (Table 2).

Table 3 shows the Spearman's rank correlation coefficients between scores. Most scores, including FACT-P domains, showed positive correlations. The coefficients between the SWB and scores, except FACT-P total and FWB, ranged from 0.04 (vs. EQ-5D-5L) to 0.18 (vs. EWB), showing very weak positive correlations.

Factors influencing health utility and HRQoL

According to the distribution of scores and scrutiny of AIC, residuals, and plots, the GLM models for EQ-5D-5L and EQ-VAS were set to the Gaussian family with identity link function. FACT-P was set to the gamma family with identity link function. Parameter estimates of statistically significant factors influencing the scores selected by stepwise methods followed by GLM model fitting are shown in Table 4. Independent variable influencing all scores measured by EQ-5D-5L, EQ-VAS, and FACT-P was ECOG PS. It was the most plausible factor negatively associated with the EQ-5D-5L (Estimate = − 0.122 for 1, − 0.164 for ≥ 2) and EQ-VAS (Estimate = − 9.658 for 1) scores. With FACT-P, living alone was the most negatively associated with the score (Estimate = − 16.741).

Discussion

This study shows health utility and HRQoL scores collected by cross-sectional surveys using generic preference-based instruments (EQ-5D-5L), VAS scores (EQ-VAS), and a non-preference-based PC-specific instrument (FACT-P) stratified by cancer progression groups. Health utility scores measured using generic instruments play an important role in evaluating the cost-effectiveness of health technologies [9]. The disease-specific FACT-P contains a 12-item PCS that addresses lifestyle issues related specifically to PC [33]. This study shows the relevance between these instruments.

Presently there are three studies that have measured health utility and HRQoL scores in Japanese PC patients. The first was published by Shimizu et al. [5] and used EQ-5D, Short Form-36 (SF-36), and time trade-off (TTO). These three methods can provide utility scores that can be used in cost-effectiveness analysis. The scores (SD) with EQ-5D, SF-36, and TTO from 330 Japanese PC patients were 0.90 (0.15), 0.89 (0.15), and 0.74 (0.08), respectively. Second, Fujimura et al. [10] obtained HRQoL scores (SD) from 82 cases of Jewett stage D2 PC and 20 cases of stage B/C PC with FACT-P, and these were 103.9 (28.3), and 120.8 (12.8), respectively. Third, Akakura et al. [7] obtained EQ-5D and VAS scores from 81 PC patients, and their paper describes correlation coefficients but not HRQoL scores. The mean score obtained in our study measured using EQ-5D-5L was smaller than that in the study by Shimizu et al. Although it was not mentioned in their paper, the EQ-5D-3L, the former version of EQ-5D-5L, may have been used because the Japanese tariff for EQ-5D-5L was developed in 2015 [23]. A systematic

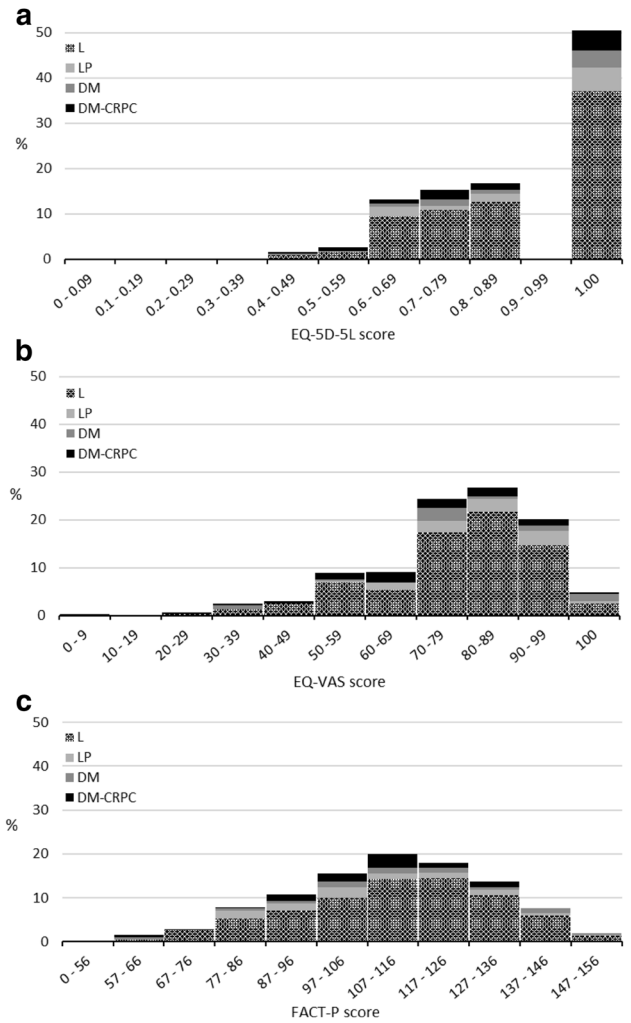

Fig. 1 Distributions of scores obtained by **a** EQ-5D-5L, **b** EQ-VAS, and **c** FACT-P. The bars of percentages of frequencies were painted separately according to cancer progression groups. The denominator of percentages for **a**, **b**, and **c** was 380, 374, and 380, respectively, due to the missing cases. *L* localized, *LP* localized progressive, *DM* distant metastatic, *DM-CRPC* distant metastatic castrate-resistant prostate cancer

review of the literature on health utility scores from 2002 to 2015, which used generic instruments, was conducted by Torvinen et al. [34]. The results of their research indicated the score varied from 0.63 to 0.91, and from 0.50 to 0.87 for localized and early stage, and advanced or metastatic stage, respectively. The results obtained in our study with generic instruments fell within the range reported by Torvinen et al. The FACT-P SWB scores reported by Fujimura et al. [10] (23.6 for stage D2, and 22.7 for B/C) were higher than those in our study (14.5 for all patients). They used the stage B/C score as a control, and it was lower than the stage D2 score; however, it did not show statistical significance ($p = 0.72$). They attributed the score of patients with D2 disease to the support and encouragement from their families. This means that the care and support from a patient's family related to disease progression and an increase in the HRQoL score. Indeed, our study showed that "living alone" status negatively affects HRQoL scores in the GLM models (Table 4). Moreover, the positive correlation among HRQoL scores includes FACT-P domains, while the SWB score showed very weak positive correlations with other instruments (Table 3). The low SWB score in our study may be due to the high number of patients living alone (7.7%; Table 1). Previous studies reported no correlation between this subscale and EQ-5D [35, 36]. In addition, it is considerable that not only living alone but also the quality of care and support may be associated with SWB. There is no gold standard for HRQoL measurements in cancer patients [37] at present. Further analysis is needed to reveal the reliable reasons for the low SWB score.

Factors affecting HRQoL scores highlighted step-wise followed by GLM are shown in Table 4. In addition to the above-mentioned "living alone" status, ECOG PS had negative statistically significant parameter estimates for scores according to all 3 instruments. The ECOG PS scale ranging from 0 (fully active) to 5 (dead) is often preferred for its

Table 3 Spearman's rank correlation coefficients between the scores

	FACT-P						EQ-VAS
	Total	Physical wellbeing	Social wellbeing	Emotional wellbeing	Functional wellbeing	PCS	
EQ-5D-5L	0.51**	0.61**	0.04	0.41**	0.41**	0.50**	0.49**
FACT-P		0.58**	0.58**	0.65**	0.79**	0.72**	0.50**
Physical wellbeing			0.05	0.48**	0.40**	0.51**	0.52**
Social wellbeing				0.18*	0.33**	0.15*	0.10*
Emotional wellbeing					0.49**	0.45**	0.39**
Functional wellbeing						0.47**	0.43**
PCS							0.49**

PCS prostate cancer subscale

Statistically significant correlation coefficients: *$p < 0.05$, **$p < 0.0001$

Table 4 Parameter estimates of statistically significant factors for the generalized linear model (GLM)

	EQ-5D-5L AIC = −360.98				EQ-VAS AIC = 2968.70				FACT-P AIC = 3117.00			
	Estimates	Standard error	*t* value	*P*[a]	Estimates	Standard error	*t* value	*P*[a]	Estimates	Standard error	*t* value	*P*[a]
ECOG performance status												
1	−0.122	0.027	−4.473	< 0.001	−9.658	2.934	−3.292	0.001	−11.193	3.097	−3.614	<0.001
≧2	−0.164	0.056	−2.913	0.004								
Living alone[b]	−0.084	0.029	−2.868	0.004					−16.741	3.159	−5.300	<0.001
Maximal CTCAE grade = 1	−0.045	0.022	−2.025	0.044								
Age	−0.003	0.001	−3.175	0.002								
Highest education												
High school					8.858	2.376	3.728	< 0.001	8.373	2.549	3.285	0.001
College or more					8.323	2.400	3. 468	< 0.001	11.569	2.604	4.443	<0.001

[a] *P* value for the two-tailed test based on the *t* value

[b] Living alone versus other living status [with wife and/or other(s)]

AIC akaike's information criterion, *ECOG* eastern cooperative oncology group [28], *CTCAE* common terminology criteria for adverse events [31]

Registered hospitals were included in models as a set of dummy variables. Negative estimates indicate that the parameters are negatively correlated to the score

simplicity and inter-observer reproducibility [28]. Age and maximal CTCAE grade were statistically significant factors only with EQ-5D-5L, but highest education (high school or more) effects the FACT-P and EQ-VAS score, not EQ-5D-5L. Although EQ-5D-5L is a generic preference-based measures providing utility scores [24], FACT-P is a PC-specific multidimensional measure [25]. This difference may be viewed as biased between disease-specific scores and others.

A strength of this study is the stratification by cancer progression groups, L, LP, DM, and DM-CRPC. In particular, the health utility score obtained in this study will be useful for cost-effectiveness analysis using QALYs as a metric. This study also has some limitations. First, the number of advanced cancer (LP, DM, DM-CRPC) patients participating in this study were smaller than L cancer patients. To confirm and detect further validated statistically significantly differences in scores between these stages, a larger sample size of advanced cancer patients is required. This study did not examine differences between groups regarding the influence of socio-demographic factors on scores. A larger sample size would make it possible to examine more detailed associations between background factors and scores. Second, patients registered in each hospital had a different tendency for disease progression (the numbers of DM-CRPC patient that participated in five hospitals were 16, 8, 6, 5 and 3, respectively). This may be due to the regional difference of the hospital and/or judgment by physicians in charge. These hospitals were all university hospitals and did not include hospitals in the north (Hokkaido and Tohoku), south (Kyusyu and Okinawa), or areas of the Sea of Japan. For valid generalization of scores obtained from this study, we must recruit patients more widely. Third, the distribution of scores obtained by EQ-5D-5L showed a strong ceiling effect (Fig. 1). It is well known that EQ-5D-3L has ceiling effects [23, 24, 38], and as a result the EQ-5D-5L was established to improve the sensitivity and reduce ceiling effect [24]. However, this improvement did not seem to completely resolve the ceiling effect [32]. In this study, EQ-5D-5L did not show statistically significant differences among disease states but significant differences were found among disease-specific FACT-P domain scores. Our results showed EQ-5D-5L is also less sensitive in prostate cancer patients. Finally, this study used self-administered questionnaires. Although not identified in this study, it is impossible to completely rule out the presence of some selection bias. If there were patients who could not answer them, they were excluded from the very beginning for practical and ethical purposes. Therefore, there is a possibility that the scores of DM-CRPC group presented here might be an overestimation.

The aim of this study was to measure health utility, VAS scores and HRQoL using EQ-5D-5L, EQ-VAS, and FACT-P among Japanese patients with PC. The scores obtained using EQ-5D-5L and EQ-VAS showed correlation with

PC-specific FACT-P score and fell within the range of a previous study from other countries (e.g., USA, Canada and UK) and multinational surveys [33]. On the other hand, scores obtained by EQ-5D-5L and FACT-P total scores showed no statistically significant differences among progression groups. As mentioned in the limitation, further additional analyses are needed to obtain clear statistical differences. Although statistically significant differences were not obtained and the differences between means of utility scores were small, the results of cost-effectiveness analysis depend on the incremental cost-effectiveness ratio (ICER) [9]. It is important to evaluate not only the improvement in utilities, but also the lower probability of disease progressions by new interventions. Applying the scores obtained in this study to cost-effectiveness analysis would necessitate performing sensitivity analyses with an appropriate wider range (i.e., 95% CI). The findings of this study stratified by progression states will help future cost-effectiveness analysis in Japanese settings. To promote implementation of cost-effectiveness analyses in Japan that the HTA system is just beginning, this research provides a foothold to accumulate useful data on quality of life research. Further research including more statistical power or patients states by specific interventions are expected for actual policy applications.

Conclusions

We obtained health utility, HRQoL, and VAS scores of L, LP, DM, and DM-CRPC patients measured using EQ-5D-5L, EQ-VAS, and FACT-P among Japanese patients with PC. To our knowledge, this is the first study evaluating health utility with the latest version of EQ-5D (5L) for Japanese PC patients. In our study, each score obtained was mutually well correlated. Our work will be useful in establishing cost-effectiveness analyses in Japanese settings where PC treatment options have increased.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in the study.

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