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Unmet needs in non-metastatic castration-resistant prostate cancer from the Japanese patient perspective: a discrete choice experiment

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Title: Unmet needs in non-metastatic castration-resistant prostate cancer from the Japanese patient perspective: a discrete choice experiment

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ABSTRACT

Objectives With novel anti-androgen treatments of different strengths and limitations becoming available, to investigate how CRPC patients value differences in treatment characteristics should be understood.

Design Cross-sectional observational study.

Setting A discrete choice experiment was conducted. Patients chose between two hypothetical nmCRPC treatments defined by six attributes: Risk of fatigue, falls or fracture, cognitive impairment, hypertension, rashes as side-effects to treatment and extension of time until cancer-related pain occurs.

Participants A total of 137 adult male CRPC patients with no prior experience with chemotherapy and with ECOG status 0 and 1 were recruited. Patients were excluded if they participated in an investigational program outside of routine clinical practice, had clinically relevant medical or psychiatric condition, or diagnosed of visceral/other metastasis not related to prostate, or were otherwise deemed ineligible by the referring physician.

Primary outcome measures Relative preference weights and relative importance of the six attributes was estimated by Hierarchical Bayesian logistic regression.

Results Among the treatment attributes, risk of cognitive impairment as a side-effect of the treatment was the most important attribute (relative importance [RI]: 27.47%, 95% confidence interval [CI]: 24.80%, 30.14%), followed by extension of time until cancer-related pain occurs (RI: 17.87%, 95% CI: 15.49%, 20.25%), and the “risk of falls or fracture” (RI: 15.99%, 95% CI: 14.73%, 17.25%). The “risk of hypertension as a side-effect of treatment” (13.77%) had similar RI as “risk of rashes as a side-effect of treatment” (13.17%), followed by the “risk of fatigue as a side-effect of treatment” (11.74%).

Conclusions Patients consider the risk of cognitive impairment as a treatment side-effect as the most important attribute in nmCRPC, followed by delaying time until pain occurs and the risk of falls and fracture. These features should be considered in treatment decision making for nmCRPC in Japan.

STRENGTHS AND LIMITATIONS

- This study applied DCE methodology to determine the relative value that patients place on different attributes of their nmCRPC treatment.
- The development of the final DCE survey encompassed a series of systematic steps including literature review, qualitative exploratory interviews, and cognitive interviews with CRPC patients.
- Although study design was meant to stimulate possible clinical decisions, this does not mean it has the same clinical meaning or emotional consequence of an actual decision, and hence, differences could arise between stated and actual response.

INTRODUCTION

Castrate-resistant prostate cancer (CRPC), defined as rising prostate-specific antigen (PSA) levels despite androgen depletion therapy (ADT), represents 10-20% of prostate cancer (PC) patients [1]. One third of CRPC patients progress to bone metastasis within two years. Bone metastases can cause significant pain and skeletal-related events and increase the risk of mortality, hence there is a need to delay or prevent progression to the metastatic state for non-metastatic CRPC (nmCRPC) patients, while maintaining the quality of patient's overall survival (OS) [2].

nmCRPC treatment options have traditionally included ADT in the form of gonadotropin-releasing hormone (GnRH) and vintage anti-androgens, and, also in this space in Japan, enzalutamide and abiraterone acetate are approved for CRPC. Hence, the recent approval of the second-generation anti-androgens apalutamide and darolutamide in nmCRPC could affect the treatment landscape. Enzalutamide and apalutamide reported extension of metastasis-free survival (MFS) [36.6 months vs. 14.7 months placebo and 40.5 months vs. 16.2 months placebo, respectively] in the primary analyses of their respective clinical trials, and have also recently reported efficacy in extending overall survival (67.0 months for enzalutamide vs. 56.3 months placebo and 73.9 months for apalutamide vs. 59.9 months placebo), based on final analyses [3–6]. They have also reported adverse effects in treatment such as fatigue (46% for enzalutamide, 33% for apalutamide, for all grades), falls (18% for enzalutamide and 22% for apalutamide) and seizures (<1% for enzalutamide and 0.2% for apalutamide, in subjects which excluded previous history of seizures) [3,4,6]. Most recently, another second generation anti-androgen, darolutamide, was also reported to extend MFS (40.4 months vs. 18.4 months for placebo), with rates of adverse events reported as falls (5.2%), fatigue (13.2%), rash (3.1%) and seizures (0.2% in subjects that included patients with previous history of seizures), and

extend overall survival (31% reduction in death compared to placebo; HR 0.69; 95% confidence interval [CI] 0.53-0.88; two-sided P=0.003) [7].

With these novel anti-androgen treatments of different strengths and limitations becoming available, it is important to understand how CRPC patients value differences in treatment characteristics. Patients' health-related preferences simply go beyond cure and are particularly cogent in situations in which several choices of optimal therapy are available [8].

This is underlined by a study in Japan which reported that prostate cancer patients preferred shared decision making with physicians and were interested to be involved in the decision making on their disease management [9]. Overall, increased patient involvement is an important part of quality improvement since it has been associated with improved health outcomes [10].

Patient preferences in CRPC have been elucidated in previous studies, showing patients valuing attributes affecting their daily quality of life (such as treatment side-effects or bone pain) over extension of survival, however most of these studies were related to metastatic CRPC treatment [11–15].

Currently there is limited information on how CRPC patients would value the differences in the attributes of treatment options in nmCRPC in Japan, hence this study aimed to investigate such.

METHODS

Study design

A discrete choice experiment (DCE) was conducted to measure nmCRPC patient's treatment preferences in Japan. It was conducted in three phases i) phase 1, the concept elicitation phase,

to elicit concepts for the development of attributes list for DCE, ii) phase 2, cognitive pre-testing phase, to solicit feedback and to determine the content validity of the draft DCE questionnaire, and iii) phase 3, final DCE paper-based survey. Survey development took place in accordance with good research practices [16] and the protocol was approved by the respective Institutional Review Boards (IRBs) of each participating institution, and by a Central IRB for institutions which did not have an in-house IRB. Informed consent was obtained from all the participants prior to any activities related to the study.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. Part of the data used in this study were obtained from patients who provided self-reported information through the survey.

Study population

Patients recruited in all phases of this study fulfilled the following inclusion criteria: i) aged 20 and above, ii) male, diagnosed with either non-metastatic or metastatic CRPC, iii) no prior experience with chemotherapy, iv) Eastern Cooperative Oncology Group (ECOG) status 0 to 1, and v) able to read and understand Japanese, and can provide informed consent and complete the survey instrument. Patients were excluded if they were participating in an investigational program with interventions outside of routine clinical practice, had a clinically-relevant medical or psychiatric condition which, in the opinion of the investigator would interfere with completing the study, a diagnosis of visceral metastasis/other metastasis not related to prostate or were otherwise deemed ineligible by the referring physician. Patients recruited in the qualitative phases (phase 1 and 2) were excluded as participants for the main DCE survey.

A target sample size of 150 patients were planned to complete the main DCE survey, which followed the common guidelines [17] and was similar to majority of the previous published studies [16].

Survey development

Survey development encompassed a series of systematic steps including literature review, qualitative exploratory interviews and cognitive interviews with CRPC patients (nmCPRC and mCRPC patients). Literature review was conducted to identify and characterize relevant treatment attributes for nmCRPC treatments using Pubmed and Embase. Attributes relating to impact on health-related quality of life (HRQoL) and efficacy were identified. Qualitative face-to-face, 60 minutes interviews were conducted in the concept elicitation phase with four nmCRPC and four mCRPC patients. Findings from this phase together with literature review were used to elicit concepts and attributes for inclusion in the draft DCE survey. The draft survey was tested in cognitive face-to-face interviews on another group of patients (4 nmCRPC and 4 mCRPC patients), and feedback from the interviews were used to finalize the DCE survey.

DCE survey

The DCE task included a series of preference-elicitation questions, each asking respondents to choose between hypothetical treatments for nmCRPC. An example of a single preference-elicitation question presented to respondents is shown in Figure 1.

The DCE was designed to collect data to estimate relative preference weights, relative importance of the attributes, and the trade-offs patients were willing to make in one attribute for changes in another attribute. In addition to the DCE choice tasks, demographic and clinical patient characteristics, as well as HRQoL measurement (EORTC QLQ-PR25) [18] were

collected from patients. Patients' prostate cancer related clinical characteristics and screening information were reported by the physicians. The experimental design of the DCE was a balanced overlap design using Sawtooth Software (Lighthouse Studio, v9.5.3). This method guaranteed that a sufficient number of patients saw the different combinations of attributes and levels and all attribute levels varied independently according to the experimental design.

Statistical analysis

The study sample was described with respect to demographics, disease history, comorbidity and HRQoL variables using frequencies and percentages for categorical variables and counts, means and standard deviations (SDs) for continuous variables.

The choice data was analyzed using hierarchical Bayesian logistic regression models with effects coding parameterization. The outcome variable of this model was choice and the predictor variables were the levels within each attribute. Point estimates of model coefficients represent mean preference weights at the aggregate level, defined as the marginal utility of a change in that attribute. With these estimates, the magnitude of the trade-offs for patients choosing among the attribute levels can be assessed. The relative importance estimates were calculated at the respondent level by dividing the range of each attribute (utility of most favorable level minus utility of least favorable level) by the sum of the ranges of all attributes. The resulting estimates are percentages, reflecting the importance of each attribute relative to the others.

The preference weights matching to each attribute level were summed for treatment profiles at the individual level. The summed preference weights of different treatment profiles were compared to determine which treatment profile would be most preferred.

The relative preference weights for each attribute level were also compared across the two subgroups: nmCRPC and mCRPC to determine whether preferences vary by patient disease status. Further analysis was conducted to examine whether preferences vary by demographics, disease and medical history, HRQoL using one-way analysis of variance (ANOVA). For all analyses, p-values < 0.05 were considered statistically significant. Analyses were performed using R 3.5.1 and SPSS 22.0.

RESULTS

Participants

A total of 137 CRPC patients, recruited from 6 participating institutions, were included in the analyses, with 60 nmCRPC and 77 mCRPC. The mean age was 75.8 (SD=7.5), 83.9% were married, 45.3% had at least 2-year college education and 30.0% were still employed. Only 7 patients (5.1%) reported being currently cared for by a primary caregiver for their PC; 42.3% of patients suffered from hypertension. The details are shown in Table 1. Patients had been diagnosed with PC for an average of 6.8 years (SD=5.2) with 56 of them (40.9%) in Stage IV M1 (metastatic) at diagnosis. 7 patients (5.1%) had experienced symptomatic skeletal-related events (SSE) since diagnosis. None of the patients were diagnosed with having seizures or cognitive impairment at the time of enrolment in the study. The details are shown in Table 2.

Table 1. Patient-reported demographics and other baseline characteristics.

		Total (N = 137)	
		N	%
Age [year] Category	<60	5	3.65%
	60-<70	20	14.60%
	70-<80	65	47.45%
	80-<90	43	31.39%
	≥90	3	2.19%

Marital status	Single	6	4.38%
	Married	115	83.94%
	Divorced	2	1.46%
	Separated	1	0.73%
	Widowed	10	7.30%
	Living with partner	2	1.46%
Level of education	Elementary school	0	0.00%
	Junior high school	23	16.79%
	High school	50	36.50%
	2-year college	4	2.92%
	4-year college	54	39.42%
	Graduate school	4	2.92%
	Decline to answer	1	0.73%
Employment status	Employed full-time	18	13.14%
	Self-employed	17	12.41%
	Part-time employed	6	4.38%
	Retired	62	45.26%
	Long-term disability	0	0.00%
	Short-term disability	0	0.00%
	Not employed (other than retired)	33	24.09%
Region of residence	Chubu	1	0.73%
	Kanto	105	76.64%
	Kyushu (including Okinawa)	30	21.90%
Household income	Less than ¥2,500,000	28	20.44%
	2,500,000 to ¥4,999,999	57	41.61%
	¥5,000,000 to ¥7,499,999	14	10.22%
	¥7,500,000 to ¥9,999,999	6	4.38%
	¥10,000,000 to ¥12,499,999	3	2.19%
	¥12,500,000 to ¥14,999,999	3	2.19%
	¥15,000,000 or more	2	1.46%
	Decline to answer	23	16.79%
Type of medical insurance	National health insurance	40	29.20%
	Late stage elderly insurance	76	55.47%
	Company/Social insurance	18	13.14%
	Welfare recipient	2	1.46%
	None of the above (all costs paid by myself/my family)	0	0.00%
Currently cared by a primary caregiver for prostate cancer	Yes	7	5.11%
	No	129	94.16%
Primary caregiver relationship	Wife	4	57.14%
	Child	1	14.29%
	Grandchild	0	0.00%
	Sibling	0	0.00%
	Other relative (parent, niece/nephew)	0	0.00%
	Hired professional caregiver	2	28.57%
	Other non-relative	0	0.00%
Physician-diagnosed comorbid condition	Cardiovascular disease	19	13.87%
	Chronic pulmonary disease	3	2.19%
	Rheumatologic disease	1	0.73%
	Peptic ulcer disease	16	11.68%
	Mild liver disease	13	9.49%
	Diabetes without chronic complications	16	11.68%

	Diabetes with chronic complications	5	3.65%
	Hemiplegia or paraplegia	1	0.73%
	Renal disease	4	2.92%
	Any malignancy, including leukemia and lymphoma	1	0.73%
	Moderate or severe liver disease	1	0.73%
	Other metastatic solid tumor currently being treated (other than that of the prostate)	1	0.73%
	AIDS/HIV	0	0.00%
	Hypertension	58	42.34%
	Prior malignancy, now in remission (malignancy other than that of the prostate)	10	7.30%
	None of the above	51	37.23%
		Mean	**SD**
Age		75.8	7.5

Table 2. Physician-reported patient clinical characteristics.

		Total (N = 137)	
		N	**%**
Prostate cancer stage at diagnosis	Stage I	2	1.46%
	Stage IIA	14	10.22%
	Stage IIB	21	15.33%
	Stage III	28	20.44%
	Stage IV M0 (no evidence of metastasis)	13	9.49%
	Stage IV M1 (metastatic)	56	40.88%
	I do not have this information	3	2.19%
Experienced since prostate cancer diagnosis	SSE	7	5.11%
	Seizure	0	0.00%
	Cognitive impairment	0	0.00%
	Patient-reported fatigue	1	0.73%
	None of the above	129	94.16%
Metastatic status of prostate cancer	Yes	77	56.20%
	No	60	43.80%
ECOG grade at study enrolment	Grade 0	106	77.37%
	Grade 1	31	22.63%
Symptomatic status at study enrolment	Symptomatic	3	2.19%
	Asymptomatic	134	97.81%
Type of the first ADT received	LHRH analog, LHRH antagonist	86	62.77%
	Surgery (Orchiectomy)	7	5.11%
	Anti-androgen	86	62.77%
	Estrogen	1	0.73%
	Progesterone	0	0.00%
	Unknown	2	1.46%
Treatment currently prescribed for prostate cancer	Abiraterone	30	21.90%
	Enzalutamide	43	31.39%

	Anti-androgens	15	10.95%
	Androgen deprivation therapy	126	91.97%
	Strontium-89	0	0.00%
	Ra-233 (Xofigo)	1	0.73%
	External beam radiotherapy	3	2.19%
	Bisphosphonate	5	3.65%
	Denosumab	29	21.17%
	Opioid	1	0.73%
	Steroid	35	25.55%
	Non-steroidal anti-inflammatory medications / paracetamol / COX-2 inhibitors	4	2.92%
	Other (nmCRPC clinical trial participant)	4	2.92%
	Other (other prostate cancer clinical trial participant)	0	0.00%
	Other	11	8.03%
	No treatment / watch and wait	2	1.46%
Treatment prescribed prior to current treatment	Abiraterone	13	11.68%
	Enzalutamide	15	20.44%
	Anti-androgens	71	76.64%
	Androgen deprivation therapy	49	75.91%
	Strontium-89	1	0.73%
	Ra-233 (Xofigo)	13	9.49%
	External beam radiotherapy	34	25.55%
	Bisphosphonate	9	8.76%
	Denosumab	20	18.98%
	Surgery	11	
	Opioid	1	10.95%
	Steroid	10	0.73%
	Non-steroidal anti-inflammatory medications / paracetamol / COX-2 inhibitors	2	9.49%
	Other (nmCRPC clinical trial participant)	6	2.19%
	Other (other prostate cancer clinical trial participant)	4	4.38%
	Other	23	3.65%
	No other treatment other than first ADT	18	16.79%
	No treatment / watch and wait	0	0.00%
		Mean	**SD**
Duration of disease (years)		6.8	5.2
Duration of metastasis (months)		50.6	41.4
Duration of CRPC (months)		24.5	17.6

Abbreviations: ADT, androgen depletion therapy; CRPC, castrate-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; nmCRPC, non-metastatic CRPC.

Attributes and levels in the DCE

The final specific attributes included in the DCE were: i) risk of fatigue as a side-effect of treatment, ii) risk of falls or fractures as a side-effect of treatment, iii) risk of cognitive

impairment as a side-effect of treatment, iv) risk of hypertension as a side-effect of treatment, v) extension of time until cancer-related pain occurs, and vi) risk of rashes as a side-effect of treatment (Supplementary table 1).

Patient preferences estimates

The hierarchical Bayesian logistic regression model results are reported in Figure 2 (and Supplementary table 2). All levels of all attributes were significantly associated with choice (all $p<0.05$). The greater the range of preference weights within an attribute, the stronger the relationship between that attribute and treatment choice.

Among the 137 CRPC patients, the "risk of cognitive impairment as a side-effect of treatment" was the most important attribute, with a relative importance (RI) of 27.47%, 95% CI: [24.80%, 30.14%]); followed by "extension of time until cancer-related pain occurs" (RI: 17.87%, 95% CI: [15.49%, 20.25%]), and the "risk of falls or fracture" (RI: 15.99%, CI: [14.73%, 17.25%]). The "risk of hypertension as a side-effect of treatment" (13.77%) had similar RI as "risk of rashes as a side-effect of treatment" (13.17%), followed by the "risk of fatigue as a side-effect of treatment" (11.74%) (Figure 3).

The RI for nmCRPC and mCRPC patients is further illustrated in Figure 4. Compared to mCRPC patients, nmCRPC patients placed more importance to risk of cognitive impairment as a side-effect of treatment (RI: 31.53% vs. 24.30%).

Based on the preference weights for attributes, summed preference weights were derived for three hypothetical treatment profiles with varying attribute levels in Table 3. Among CRPC patients, treatment profile I, with the lowest risk of side-effects, had significantly higher summed preference weights mean (mean [95% CI]: 3.23 [2.91, 3.56] vs. -2.09 [-2.30, -1.88] vs. -0.062 [-0.15, 0.026]), compared to the other two treatment profiles. The results were

similar for both nmCRPC and mCRPC subgroups, in that majority of patients would prefer the profile with the lowest risk of side-effects.

Table 3. Summary of patient preference for different treatment profiles

		Treatment Profile I	Treatment Profile II	Treatment Profile III
Attribute levels	Risk of fatigue as a side-effect of treatment	15%	25%	35%
	Risk of falls or fracture as a side-effect of treatment	3%	20%	10%
	Risk of cognitive impairment as a side-effect of treatment	0%	5%	5%
	Risk of hypertension as a side-effect of treatment	5%	25%	15%
	Extension of time until cancer-related pain occurs	15 months	35 months	35 months
	Risk of rashes as a side-effect of treatment	5%	25%	15%
CRPC	Summed preference weights: Mean (95% CI)	3.234 (2.905, 3.563)	-2.088 (-2.296, -1.880)	-0.062 (-0.149, 0.026)
	Patients in favour of the profile: N (%)	128 (93.4%)	2 (1.5%)	7 (5.1%)
mCRPC	Summed preference weights: Mean (95% CI)	3.226 (2.776, 3.675)	-2.141 (-2.420, -1.861)	-0.151 (-0.268, -0.034)
	Patients in favour of the profile: N (%)	72 (93.5%)	1 (1.3%)	4 (5.2%)
nmCRPC	Summed preference weights: Mean (95% CI)	3.245 (2.758, 3.732)	-2.020 (-2.334, -1.706)	0.053 (-0.073, 0.179)
	Patients in favour of the profile: N (%)	56 (93.3%)	1 (1.7%)	3 (5.0%)

Abbreviations: CRPC, castrate-resistant prostate cancer; nmCRPC, non-metastatic CRPC.

Patient preferences by demographic, health history, and HRQoL

No significant differences in preferences weights were observed when comparing across demographic and health history variables (Supplementary table 3), nor was there any significant association between patient HRQoL and treatment preference (Supplementary table 4).

DISCUSSION

Dedicated qualitative interviews and DCEs play an important role in understanding and assessing patient's priorities in selecting available treatment options. DCEs have been used to elicit patient preferences in many other therapeutic fields as well as for prostate cancer [19–

24]. This study also applied DCE methodology to determine the relative value that patients place on different attributes of their nmCRPC treatment. Our results suggest that CRPC patients (both nmCRPC and mCRPC) preferred safer treatment profiles with lesser risk of adverse events, given that most chose a hypothetical treatment profile with the least risk of side-effects. This is consistent with previous studies reporting that avoiding side-effects is relatively important to CRPC patients when considering treatment options [11,12]. In our study, CRPC patients considered the risk of cognitive impairment as a side-effect of treatment as the most important treatment attribute in nmCRPC, followed by extension of time until cancer-related pain occurs. Furthermore, patients were willing to trade-off effectiveness such as time until pain occurs for lower risk of side-effects such as cognitive impairment. Our results are also consistent with recent patient preference studies on CRPC treatment which reported cognition and memory problems as being relatively more important than other treatment attributes [12,25].

The impact on cognition and cognitive impairment in older adults with cancer has been reported, and it is thought that the triple conditions of aging, cancer and cancer treatment can negatively affect cognition [26]. In prostate cancer, a meta-analysis by McGinty *et al*. showed that patients who received ADT performed significantly worse on visuomotor tasks compared to non-cancer control groups, and they noted that these findings are consistent with the known effects of testosterone on cognitive functioning in healthy men [27]. Any factor influencing cognition, therefore, is of great importance for the nmCRPC patients due to possibly relatively long period of ADT even prior to CRPC. Furthermore, in the nmCRPC state, patients are largely asymptomatic [28], and having cognitive impairment may greatly affect their ability to function independently, hence compromising their quality of life. Indeed, a study on Japanese community-dwelling older adults, showed that even mild cognitive impairment may be related to an increased risk for the development of disability in the future [29].

Looking at the degree of relative importance that mCRPC and nmCRPC patients separately placed on these two attributes, nmCRPC patients weighed more on risk of cognitive impairment while mCRPC patients weighed more on extension of time until cancer-related pain occurs. The difference in the degree of importance could be associated with most nmCRPC patients being asymptomatic, hence, accordingly, with a long duration of hormonal therapy, patients would want to spend their daily lives with a well-maintained QoL that precludes an increased risk of cognitive impairment while on treatment. As well, for mCRPC patients, due to increased age, the advanced stage of disease, and having experienced more bone metastasis-related pain, the importance of pain management to maintain QoL in the time they have left is understandable. In a qualitative study on pain in CRPC with bone metastasis, patients reported that bone pain was the most prominent and debilitating symptom associated with their condition, while another study found that bone pain was found to be the strongest predictor of skeletal related events, which are linked with a reduced quality of life and worse outcomes [30,31].

These results are, furthermore, congruent to a study by Nakayama *et al.,* which showed the differences in the patients' treatment preferences across different PC stages wherein patients with more advanced PC would prefer efficacy, whereas patients in less advanced PC would prefer maintenance of HRQoL[23]. Our study reflects a similar trend where the patients' preference reflects a mixture of putting more emphasis on efficacy (mCRPC) and on safety and tolerability (nmCRPC), with patients wanting to protect their QoL via an implied need to delay cognitive side-effects, as well as delaying cancer-related pain.

The need of Japanese patients for minimal side-effects while receiving effective nmCPRC therapy, as reflected in their preferences for safer treatment features, should be considered in treatment decision making. In Japan, new anti-androgens are available as nmCRPC treatments, with each treatment having its own reported central nervous system related features such as

cognitive impairment and efficacy in delaying pain progression, among others. A better awareness of attributes that influence patients' treatment decision may enable clinicians to communicate with patients more effectively when making shared decisions on CRPC treatment strategies.

Finally, we compared the results here with a physician preference study done in parallel with this study, and physicians were also asked about their preferences for the same set of attributes. From the physician perspective, "Extension of time until cancer-related pain occurs" were the most important, followed by "Risk of falls or fracture as a side effect of treatment". However, "Risk of cognitive impairment as a side effect of treatment" ranked only 4th in terms of attribute relative importance, showing a gap in how patients and physicians perceive treatment attributes in nmCRPC (Figure 5). The gap in patients' perception of nmCRPC treatment attributes versus that of physicians emphasizes the need for open communication of treatment benefits and risks between patients and their physicians. In previous studies on gaps between patients and physicians' preferences in prostate cancer, different reasons for such gaps have been put forward, such as the structure of patient-physician encounters being typically physician-driven, or that physicians may judge patients' health using different reference points from their clinical practice experience [32,33]. Clinical decision making could be balanced by asking patients' regarding their personal preferences about treatment risks and benefits to establish patient-centered care.

A few limitations of this study should be noted. Due to sample selection during recruitment, respondents who were healthy enough to participate and were interested in research may be over-represented, hence could potentially introduce selection bias. Their responses in the DCE was towards hypothetical treatment profiles. One of the key aspects of this design was to stimulate possible clinical decisions, but this does not mean it has the same clinical meaning or emotional consequence of an actual decision. Hence, differences could arise between stated

and actual response. Potential hypothetical bias can be limited by constructing choice questions that mimic realistic clinical choices as closely as possible and map clearly into clinical evidence. Although not central to the research questions, a few of our potential covariates (e.g., comorbidities) were reported directly from the patient without clinical verification. This decision was made to ease the burden on the physician investigators though it does introduce possible additional measurement error in the assessment of these variables.

CONCLUSION

Patients value safety and prioritize central nervous system related features such as lower risk of cognitive impairment and extension of time until pain occurs when choosing among nmCRPC treatment options with similar efficacy but different safety profiles. Such an assessment provides insights into the patients' nmCRPC treatment preferences and taking them into consideration will help physicians when developing their treatment strategies for their patients in Japan.

AUTHOR CONTRIBUTIONS

Hiroji Uemura contributed input to the study design as expert opinion leader, as well as to data collection and interpretation of the results. Hisashi Matsushima, Akira Yokomizo, Kazuki Kobayashi, Gaku Arai, and Takefumi Satoh were responsible for data collection and interpretation of study results. Vince Grillo, Shikha Singh and Yirong Chen were responsible for study design, data aggregation and analysis, study coordination, and medical writing. Dianne Athene Ledesma was responsible for creating the study design, data interpretation, and overall coordination of the study. All authors read and approved the final manuscript.

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COMPETING INTEREST

Dianne Athene Ledesma is an employee of Bayer Yakuhin, Ltd. Vince Grillo, Shikha Singh and Yirong Chen are employees of Kantar, Health Division.

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FIGURE LEGENDS

Figure 1. Example of preference-elicitation task.

Figure 2. Attribute-level preference weights: overall sample (N=137).

Figure 3. Relative importance of treatment attributes: overall sample (N=137).

Figure 4. Relative importance of treatment attributes: nmCRPC vs. mCRPC.

Figure 5. Relative importance of treatment attributes: patients vs. physicians.

Figure 1. Example of preference-elicitation task.

30x34mm (300 x 300 DPI)

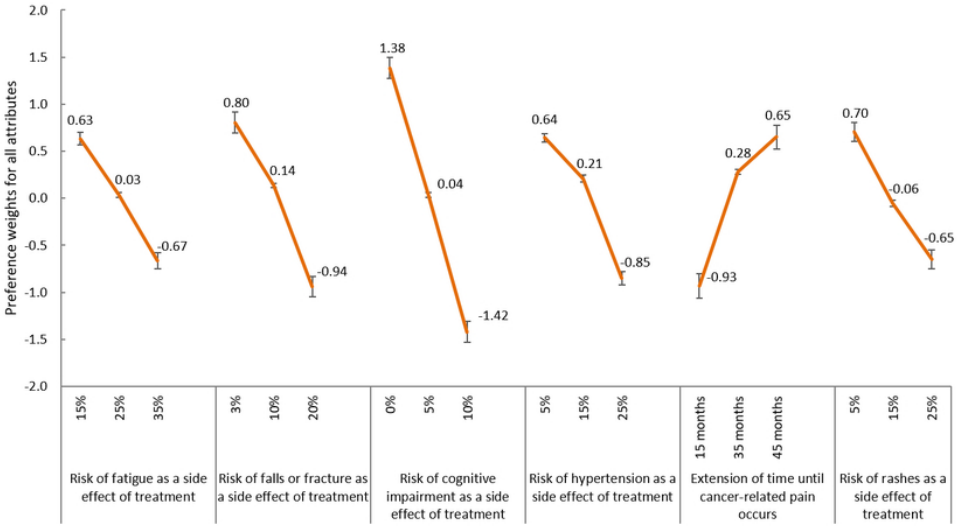

Figure 2. Attribute-level preference weights: overall sample (N=137).

72x39mm (300 x 300 DPI)

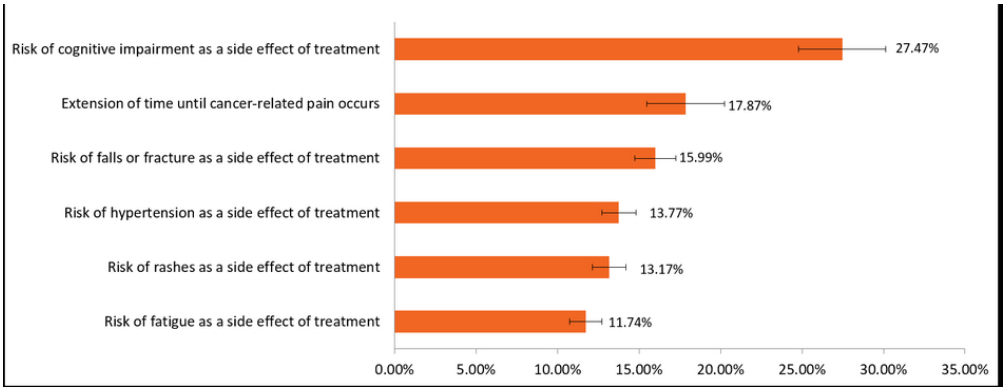

Figure 3. Relative importance of treatment attributes: overall sample (N=137).

80x30mm (300 x 300 DPI)

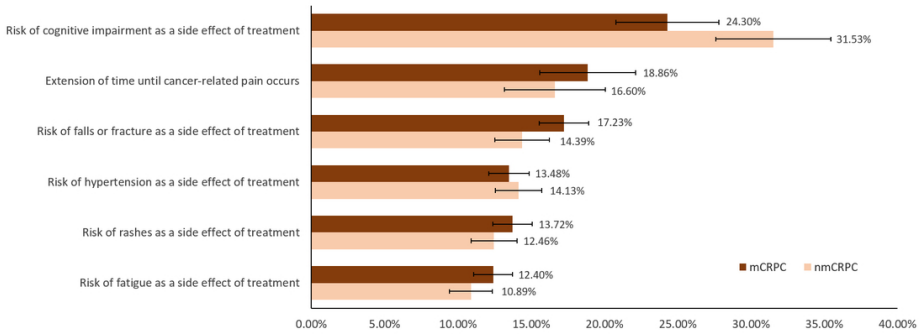

Figure 4. Relative importance of treatment attributes: nmCRPC vs. mCRPC.

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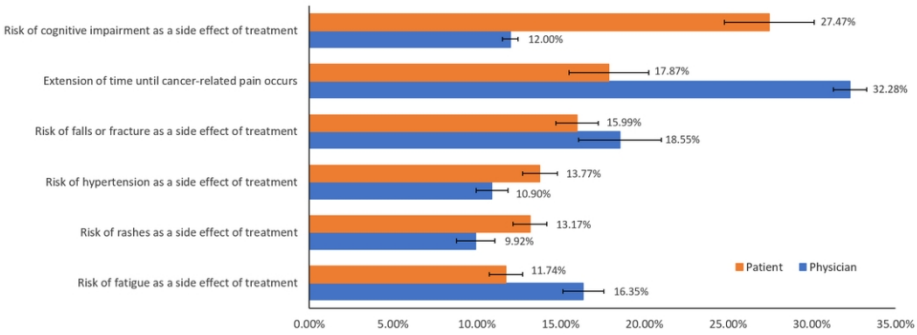

Figure 5. Relative importance of treatment attributes: patients vs. physicians.

100x35mm (300 x 300 DPI)

Supplementary material

Supplementary table 1 List of attributes and levels in DCE

Attributes	Levels
i. Risk of fatigue as a side-effect of treatment	• 15% • 25% • 35%
ii. Risk of falls or fractures as a side-effect of treatment	• 3% • 10% • 20%
iii. Risk of cognitive impairment as a side-effect of treatment	• 0% • 5% • 10%
iv. Risk of hypertension as a side-effect of treatment	• 5% • 15% • 25%
v. Extension of time until cancer-related pain occurs	• 15 months • 35 months • 45 months
vi. Risk of rashes as a side-effect of treatment	• 5% • 15% • 25%

Supplementary table 2 Attribute-level preference weights: overall sample (N=137)

Attribute	Levels	Mean preference weight	SE	95% CI	p-value
Risk of fatigue as a side-effect of treatment	15%	0.633	0.035	0.564, 0.703	<0.001
	25%	0.034	0.013	0.009, 0.059	0.009
	35%	-0.667	0.043	-0.752, -0.582	<0.001
Risk of falls or fracture as a side- effect of treatment	3%	0.802	0.057	0.691, 0.913	<0.001
	10%	0.136	0.013	0.110, 0.161	<0.001
	20%	-0.938	0.054	-1.044, -0.831	<0.001
Risk of cognitive impairment as a side-effect of treatment	0%	1.385	0.058	1.271, 1.498	<0.001
	5%	0.035	0.012	0.012, 0.059	0.005
	10%	-1.420	0.056	-1.530, -1.310	<0.001
Risk of hypertension as a side-effect of treatment	5%	0.642	0.024	0.595, 0.689	<0.001
	15%	0.210	0.018	0.173, 0.246	<0.001
	25%	-0.852	0.037	-0.925, -0.779	<0.001
Extension of time until cancer-related pain occurs	15 months	-0.933	0.068	-1.066, -0.799	<0.001
	35 months	0.281	0.015	0.252, 0.309	<0.001
	45 months	0.652	0.064	0.526, 0.778	<0.001
Risk of rashes as a side-effect of treatment	5%	0.705	0.050	0.606, 0.803	<0.001
	15%	-0.056	0.016	-0.088, -0.024	<0.001
	25%	-0.648	0.051	-0.749, -0.548	<0.001

Supplementary table 3 Differences in preference weights across demographic and health history factors

			Risk of fatigue as a side-effect of treatment			Risk of falls or fracture as a side-effect of treatment			Risk of cognitive impairment as a side-effect of treatment			Risk of hypertension as a side-effect of treatment			Extension of time until cancer-related pain occurs			Risk of rashes as a side-effect of treatment		
		N	15%	25%	35%	3%	10%	20%	0%	5%	10%	5%	15%	25%	15 months	35 months	45 months	5%	15%	25%
Age group	<60	5	0.468	0.045	-0.513	0.429	0.123	-0.552	1.453	-0.083	-1.370	0.545	0.124	-0.569	-1.220	0.251	0.969	0.409	-0.093	-0.316
	60-<70	20	0.617	0.024	-0.641	0.755	0.170	-0.925	1.465	0.007	-1.472	0.646	0.174	-0.820	-1.015	0.274	0.741	0.728	-0.078	-0.651
	70-<80	65	0.620	0.021	-0.641	0.789	0.138	-0.927	1.362	0.055	-1.417	0.657	0.183	-0.840	-0.999	0.283	0.716	0.736	-0.037	-0.700
	≥80	46	0.691	0.059	-0.750	0.897	0.116	-1.013	1.353	0.031	-1.384	0.635	0.273	-0.908	-0.775	0.283	0.492	0.690	-0.074	-0.616
	p-value		0.621	0.602	0.595	0.455	0.621	0.479	0.922	0.119	0.966	0.849	0.096	0.098	0.380	0.978	0.297	0.683	0.689	0.548
Marital status	Married / Living with partner	117	0.646	0.034	-0.680	0.827	0.135	-0.961	1.373	0.043	-1.415	0.644	0.203	-0.847	-0.948	0.284	0.664	0.732	-0.060	-0.672
	Not	20	0.586	0.043	-0.629	0.686	0.135	-0.822	1.407	-0.012	-1.395	0.642	0.249	-0.891	-0.846	0.260	0.586	0.558	-0.040	-0.518
	p-value		0.558	0.797	0.687	0.394	0.980	0.377	0.837	0.113	0.902	0.975	0.396	0.612	0.608	0.568	0.679	0.234	0.681	0.303
Level of education	Completed university education	62	0.628	0.029	-0.657	0.785	0.141	-0.925	1.423	0.035	-1.457	0.625	0.219	-0.844	-0.899	0.290	0.609	0.699	-0.053	-0.646
	Not	75	0.647	0.040	-0.686	0.826	0.130	-0.956	1.339	0.035	-1.375	0.659	0.202	-0.862	-0.963	0.273	0.690	0.715	-0.061	-0.654
	p-value		0.790	0.677	0.733	0.721	0.681	0.784	0.476	0.970	0.467	0.487	0.656	0.832	0.640	0.566	0.532	0.879	0.821	0.939
Employment status	Employed	41	0.706	0.047	-0.753	0.879	0.149	-1.028	1.358	0.024	-1.382	0.667	0.228	-0.895	-0.994	0.279	0.714	0.740	-0.058	-0.682
	Not employed	96	0.609	0.030	-0.638	0.776	0.128	-0.905	1.386	0.040	-1.426	0.634	0.202	-0.836	-0.908	0.281	0.627	0.694	-0.057	-0.636
	p-value		0.211	0.533	0.228	0.409	0.476	0.301	0.824	0.555	0.723	0.532	0.531	0.446	0.569	0.945	0.536	0.675	0.989	0.685
Household income	Less than ¥5,000,000	85	0.644	0.037	-0.681	0.817	0.148	-0.965	1.413	0.038	-1.451	0.642	0.220	-0.862	-0.849	0.284	0.566	0.699	-0.051	-0.647
	¥5,000,000 to ¥9,999,999	20	0.660	0.062	-0.722	0.786	0.080	-0.866	1.263	0.019	-1.282	0.699	0.267	-0.966	-0.917	0.248	0.669	0.682	-0.040	-0.642
	¥10,000,000 or more	8	0.797	0.019	-0.816	1.191	0.090	-1.281	0.975	0.115	-1.090	0.669	0.150	-0.819	-1.453	0.398	1.055	0.864	-0.148	-0.717
	Decline to answer	24	0.540	0.010	-0.550	0.656	0.150	-0.807	1.486	0.010	-1.497	0.595	0.144	-0.739	-1.080	0.258	0.823	0.707	-0.063	-0.644
	p-value		0.468	0.701	0.533	0.274	0.253	0.297	0.237	0.297	0.335	0.677	0.227	0.388	0.164	0.177	0.206	0.893	0.571	0.991
Type of medical insurance	National health insurance	40	0.605	0.022	-0.627	0.746	0.137	-0.883	1.408	0.044	-1.452	0.628	0.196	-0.824	-0.989	0.272	0.718	0.685	-0.026	-0.659
	Late stage elderly insurance	76	0.677	0.040	-0.717	0.875	0.129	-1.004	1.348	0.047	-1.396	0.648	0.226	-0.874	-0.879	0.294	0.586	0.731	-0.070	-0.662
	Company/Social insurance	18	0.505	0.009	-0.513	0.587	0.163	-0.749	1.484	-0.029	-1.455	0.634	0.158	-0.793	-1.095	0.252	0.843	0.592	-0.067	-0.525
	Welfare recipient	2	1.017	0.342	-1.359	1.428	0.058	-1.486	0.904	-0.023	-0.880	0.894	0.343	-1.236	-0.445	0.225	0.221	1.292	-0.125	-1.167
	p-value		0.214	0.022	0.094	0.181	0.749	0.245	0.651	0.175	0.666	0.635	0.505	0.538	0.573	0.737	0.444	0.418	0.645	0.518

Currently cared by a primary caregiver for prostate cancer	Yes	7	0.665	0.058	-0.723	0.815	0.046	-0.861	1.137	0.071	-1.208	0.582	0.301	-0.862	-1.021	0.307	0.714	0.575	-0.062	-0.513
	No	129	0.636	0.034	-0.670	0.807	0.139	-0.946	1.390	0.033	-1.424	0.647	0.205	-0.852	-0.929	0.279	0.650	0.715	-0.057	-0.658
	p-value		0.858	0.678	0.789	0.975	0.116	0.731	0.334	0.480	0.398	0.551	0.254	0.838	0.769	0.681	0.827	0.542	0.944	0.536
Duration of prostate cancer (median split)	≤5 years	76	0.619	0.024	-0.643	0.808	0.135	-0.943	1.365	0.035	-1.401	0.635	0.197	-0.832	-0.994	0.295	0.699	0.700	-0.067	-0.633
	>5 years	60	0.662	0.049	-0.711	0.806	0.135	-0.941	1.393	0.035	-1.427	0.655	0.226	-0.852	-0.858	0.262	0.596	0.717	-0.045	-0.672
	p-value		0.553	0.337	0.443	0.984	0.990	0.986	0.815	0.969	0.815	0.676	0.427	0.838	0.327	0.270	0.431	0.867	0.511	0.709
ECOG grade at study enrolment	Grade 0	105	0.631	0.027	-0.658	0.811	0.135	-0.946	1.373	0.036	-1.409	0.639	0.205	-0.832	-0.973	0.282	0.690	0.719	-0.058	-0.661
	Grade 1	31	0.662	0.062	-0.724	0.796	0.132	-0.928	1.392	0.031	-1.423	0.661	0.227	-0.838	-0.802	0.275	0.527	0.669	-0.056	-0.613
	p-value		0.718	0.252	0.528	0.915	0.922	0.893	0.888	0.847	0.917	0.701	0.609	0.838	0.299	0.830	0.293	0.680	0.970	0.695
Symptomatic status at study enrolment	Symptomatic	3	0.853	-0.081	-0.772	0.979	0.097	-1.076	0.755	0.081	-0.836	0.547	0.124	-0.838	-1.990	0.252	1.739	1.039	-0.210	-0.829
	Asymptomatic	133	0.633	0.038	-0.671	0.803	0.136	-0.939	1.391	0.034	-1.425	0.646	0.212	-0.838	-0.910	0.281	0.629	0.700	-0.054	-0.646
	p-value		0.364	0.171	0.734	0.651	0.667	0.713	0.107	0.563	0.123	0.548	0.489	0.838	0.020	0.768	0.011	0.324	0.165	0.603

Supplementary table 4 Regression coefficients for preference weights and HRQoL sub-scale scores

		Risk of fatigue as a side-effect of treatment			Risk of falls or fracture as a side-effect of treatment			Risk of cognitive impairment as a side-effect of treatment			Risk of hypertension as a side-effect of treatment			Extension of time until cancer-related pain occurs			Risk of rashes as a side-effect of treatment		
	N	15%	25%	35%	3%	10%	20%	0%	5%	10%	5%	15%	25%	15 months	35 months	45 months	5%	15%	25%
Symptom scale: Urinary symptoms	137	0.002	0.000	-0.001	-0.001	0.001	0.000	0.003	0.000	-0.003	-0.001	0.002	-0.001	0.004	-0.001	-0.004	-0.001	0.000	0.001
p-value		0.455	0.896	0.567	0.848	0.500	0.970	0.375	0.865	0.380	0.367	0.065	0.745	0.291	0.530	0.329	0.722	0.938	0.709
Symptom item: Incontinence aid	36	-0.004	-0.001	0.006	-0.007	-0.002	0.009	-0.001	-0.001	0.002	-0.004	-0.003	0.004	-0.005	0.000	0.005	-0.009	-0.001	0.010
p-value		0.022	0.052	0.012	0.020	0.103	0.003	0.741	0.148	0.519	0.011	0.545	0.060	0.249	0.596	0.247	0.002	0.524	0.002
Symptom scale: Bowel symptoms	137	-0.004	-0.001	0.004	-0.007	-0.001	0.009	0.004	-0.001	-0.003	-0.005	0.002	0.003	0.006	0.001	-0.007	-0.011	-0.001	0.012
p-value		0.256	0.603	0.280	0.144	0.217	0.068	0.428	0.564	0.487	0.020	0.233	0.368	0.303	0.366	0.195	0.013	0.370	0.006
Symptom scale: Hormonal treatment-related symptoms	137	0.004	0.000	-0.004	0.004	0.000	-0.003	-0.001	0.001	0.000	-0.002	0.000	0.002	0.001	0.003	-0.004	-0.002	0.000	0.002
p-value		0.148	0.908	0.224	0.422	0.725	0.451	0.894	0.472	0.988	0.315	0.834	0.486	0.800	0.036	0.460	0.608	0.908	0.590
Functional scales: Sexual activity	137	-0.002	0.000	0.003	-0.004	0.000	0.005	0.001	-0.003	0.002	-0.004	-0.003	0.007	-0.002	-0.001	0.003	-0.002	-0.002	0.004
p-value		0.587	0.852	0.619	0.546	0.843	0.498	0.850	0.054	0.835	0.227	0.131	0.127	0.830	0.734	0.761	0.716	0.367	0.519
Functional scales: Sexual functioning	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	17-18
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	12-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Unmet needs in non-metastatic castration-resistant prostate cancer from the Japanese patient perspective: a discrete choice experiment

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Title: Unmet needs in non-metastatic castration-resistant prostate cancer from the Japanese patient perspective: a discrete choice experiment

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ABSTRACT

Objectives With novel anti-androgen treatments of different strengths and limitations becoming available, to investigate how castrate-resistant prostate cancer (CRPC) patients value differences in treatment characteristics.

Design Cross-sectional observational study.

Setting A discrete choice experiment was conducted. Patients chose between two hypothetical non-metastatic CRPC (nmCRPC) treatments defined by six attributes: Risk of fatigue, falls or fracture, cognitive impairment, hypertension, rashes as side-effects to treatment and extension of time until cancer-related pain occurs.

Participants A total of 137 adult male CRPC patients with no prior experience with chemotherapy and with ECOG status 0 and 1 were recruited. Patients were excluded if they participated in an investigational program outside of routine clinical practice, had clinically relevant medical or psychiatric condition, or diagnosed of visceral/other metastasis not related to prostate, or were otherwise deemed ineligible by the referring physician.

Primary outcome measures Relative preference weights and relative importance of the six attributes was estimated by Hierarchical Bayesian logistic regression.

Results Among the treatment attributes, risk of cognitive impairment as a side-effect of the treatment was the most important attribute (relative importance (RI) [95% confidence interval]: 27.47% [24.80%, 30.14%]), followed by extension of time until cancer-related pain occurs (RI: 17.87% [15.49%, 20.25%]), and the "risk of falls or fracture" (RI: 15.99% [14.73%, 17.25%]). The "risk of hypertension as a side-effect of treatment" (RI: 13.77% [12.73%, 14.81%]) had similar RI as "risk of rashes as a side-effect of treatment" (RI: 13.17% [12.15%, 14.19%]), followed by the "risk of fatigue as a side-effect of treatment" (RI: 11.74% [10.75%, 12.73%]).

Conclusions Patients consider the risk of cognitive impairment as a treatment side-effect as the most important attribute in nmCRPC, followed by delaying time until pain occurs and the risk of falls and fracture. These features should be considered in treatment decision making for nmCRPC in Japan.

STRENGTHS AND LIMITATIONS

- A major strength of this study is the application of the DCE methodology to determine the relative value that patients place on different attributes of their nmCRPC treatment.
- Another strength lies in the development of the final DCE survey, which encompassed a series of systematic steps including literature review, qualitative exploratory interviews, and cognitive interviews with CRPC patients.
- A limitation is the representativeness of the CRPC patients included in this study, who were a convenient sample recruited from a few selected facilities in Japan.
- Another limitation is that the DCE design may not have the same clinical meaning or emotional consequence of an actual treatment decision.

INTRODUCTION

Castrate-resistant prostate cancer (CRPC), defined as rising prostate-specific antigen (PSA) levels despite androgen depletion therapy (ADT), represents 10-20% of prostate cancer (PC) patients [1]. One third of CRPC patients progress to bone metastasis within two years. Bone metastases can cause significant pain and skeletal-related events and increase the risk of mortality, hence there is a need to delay or prevent progression to the metastatic state for non-metastatic CRPC (nmCRPC) patients, while maintaining the quality of patient's overall survival (OS) [2].

nmCRPC treatment options have traditionally included ADT in the form of gonadotropin-releasing hormone (GnRH) and vintage anti-androgens, and, also in this space in Japan, enzalutamide and abiraterone acetate are approved for CRPC. Hence, the recent approval of the second-generation anti-androgens apalutamide and darolutamide in nmCRPC could affect the treatment landscape. Enzalutamide and apalutamide reported extension of metastasis-free survival (MFS) [36.6 months vs. 14.7 months placebo and 40.5 months vs. 16.2 months placebo, respectively] in the primary analyses of their respective clinical trials, and have also recently reported efficacy in extending overall survival (67.0 months for enzalutamide vs. 56.3 months placebo and 73.9 months for apalutamide vs. 59.9 months placebo), based on final analyses [3–6]. They have also reported adverse effects in treatment such as fatigue (46% for enzalutamide, 33% for apalutamide, for all grades), falls (18% for enzalutamide and 22% for apalutamide) and seizures (<1% for enzalutamide and 0.2% for apalutamide, in subjects which excluded previous history of seizures) [3,4,6]. Most recently, another second generation anti-androgen, darolutamide, was also reported to extend MFS (40.4 months vs. 18.4 months for placebo), with rates of adverse events reported as falls (5.2%), fatigue (13.2%), rash (3.1%) and seizures (0.2% in subjects that included patients with previous history of seizures), and

extend overall survival (31% reduction in death compared to placebo; HR 0.69; 95% confidence interval [CI] 0.53-0.88; two-sided P=0.003) [7].

With these novel anti-androgen treatments of different strengths and limitations becoming available, it is important to understand how CRPC patients value differences in treatment characteristics. Patients' health-related preferences simply go beyond cure and are particularly cogent in situations in which several choices of optimal therapy are available [8].

This is underlined by a study in Japan which reported that prostate cancer patients preferred shared decision making with physicians and were interested to be involved in the decision making on their disease management [9]. Overall, increased patient involvement is an important part of quality improvement since it has been associated with improved health outcomes [10].

Patient preferences in CRPC have been elucidated in previous studies, showing patients valuing attributes affecting their daily quality of life (such as treatment side-effects or bone pain) over extension of survival, however most of these studies were related to metastatic CRPC treatment [11–15].

Currently there is limited information on how CRPC patients would value the differences in the attributes of treatment options in nmCRPC in Japan, hence this study aimed to investigate such.

METHODS

Study design

A discrete choice experiment (DCE) was conducted to measure nmCRPC patient's treatment preferences in Japan. It was conducted in three phases i) phase 1, the concept elicitation phase,

to elicit concepts for the development of attributes list for DCE, ii) phase 2, cognitive pre-testing phase, to solicit feedback and to determine the content validity of the draft DCE questionnaire, and iii) phase 3, final DCE paper-based survey. Survey development took place in accordance with good research practices [16]. The protocol was approved by the respective Institutional Review Boards (IRBs) of each participating institution: Yokohama City University Ethical Committee (Approval No. B181004003 for Yokohama City University Medical Center), Tokyo Metropolitan Hospital Clinical Research Evaluation Committee (Approval No. 19-a08 for Tokyo Metropolitan Hospital), Harasanshin Hospital Ethical Committee (Approval No. 2019-03 for Harasanshin Hospital), Dokkyo Medical University Saitama Medical Center Clinical Research Ethical Review Committee (Approval No. 1915 for Dokkyo Medical University Saitama Medical Center), Yokosuka Kyosai Hospital Clinical Research Ethical Review Committee (Approval No. 19-7 for Yokosuka Kyosai Hospital); and by a Central IRB (NPO Clinical Research Support Network Japan, Approval No. 20131) for Satoh Takefumi Prostate Clinic which did not have an in-house IRB. The participating institutions were selected to ensure representativeness in terms of geographic distribution in Japan. Informed consent was obtained from all the participants prior to any activities related to the study.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. Part of the data used in this study were obtained from patients who provided self-reported information through the survey.

Study population

Patients recruited in all phases of this study fulfilled the following inclusion criteria: i) aged 20 and above, ii) male, diagnosed with either non-metastatic or metastatic CRPC, iii) no prior

experience with chemotherapy, iv) Eastern Cooperative Oncology Group (ECOG) status 0 to 1, and v) able to read and understand Japanese, and can provide informed consent and complete the survey instrument. Patients were excluded if they were participating in an investigational program with interventions outside of routine clinical practice, had a clinically-relevant medical or psychiatric condition which, in the opinion of the investigator would interfere with completing the study, a diagnosis of visceral metastasis/other metastasis not related to prostate or were otherwise deemed ineligible by the referring physician. Patients recruited in the qualitative phases (phase 1 and 2) were excluded as participants for the main DCE survey. For the quantitative phase, a consecutive, convenience sample of patients were recruited from each participating institution, to account for potential variations in treatment patterns, scheduling of hospital visits, and the size and general health of the population of interest.

A target sample size of 150 patients were planned to complete the main DCE survey. Each respondent was planned to answer ten preference-elicitation questions choosing between two hypothetical treatments defined by six attributes, which followed the common guidelines and rule-of-thumb for the sample size in DCE studies [17] and was similar to majority of the previous published studies [16]. The sample size fulfilled the recommendation of maximum standard error of 0.05 [18] based on simulation and was deemed feasible to recruit in Japan.

Survey development

Survey development encompassed a series of systematic steps including literature review, qualitative exploratory interviews and cognitive interviews with CRPC patients (nmCPRC and mCRPC patients). Literature review was conducted to identify and characterize relevant treatment attributes for nmCRPC treatments using Pubmed and Embase. Attributes relating to impact on health-related quality of life (HRQoL) and efficacy were identified. Qualitative face-to-face, 60 minutes interviews were conducted in the concept elicitation phase with four

nmCRPC and four mCRPC patients. Findings from this phase together with literature review were used to elicit concepts and attributes for inclusion in the draft DCE survey. The draft survey was tested in cognitive face-to-face interviews on another group of patients (4 nmCRPC and 4 mCRPC patients), and feedback from the interviews were used to finalize the DCE survey.

DCE survey

The DCE task included a series of preference-elicitation questions, each asking respondents to choose between hypothetical treatments for nmCRPC. An example of a single preference-elicitation question presented to respondents is shown in Figure 1.

The DCE was designed to collect data to estimate relative preference weights, relative importance of the attributes, and the trade-offs patients were willing to make in one attribute for changes in another attribute. In addition to the DCE choice tasks, demographic and clinical patient characteristics, as well as HRQoL measurement (EORTC QLQ-PR25) [19] were collected from patients. Patients' prostate cancer related clinical characteristics and screening information were reported by the physicians. The experimental design of the DCE was a balanced overlap design using Sawtooth Software (Lighthouse Studio, v9.5.3), targeted only the main effect of the attributes. This method guaranteed that a sufficient number of patients saw the different combinations of attributes and levels and all attribute levels varied independently according to the experimental design. The design of the DCE in this study featured eight blocks of ten preference-elicitation questions and each patient was given one block of questions. In addition, each patient was also given a hold-out question containing two treatment profiles with the absolute best-case scenario and the absolute worst-case scenario to assess and assure comprehension of the DCE.

Statistical analysis

The study sample was described with respect to demographics, disease history, comorbidity and HRQoL variables using frequencies and percentages for categorical variables and counts, means and standard deviations (SDs) for continuous variables.

The choice data was analyzed using hierarchical Bayesian logistic regression models with effects coding parameterization (the third level being the base level) and non-informative priors for the parameters, using *rjags* package in R [20]. The outcome variable of this model was choice and the predictor variables were the levels within each attribute. Point estimates of model coefficients represent mean preference weights at the aggregate level, defined as the marginal utility of a change in that attribute. With these estimates, the magnitude of the trade-offs for patients choosing among the attribute levels can be assessed. The relative importance estimates were calculated at the respondent level by dividing the range of each attribute (utility of most favorable level minus utility of least favorable level) by the sum of the ranges of all attributes. The resulting estimates are percentages, reflecting the importance of each attribute relative to the others.

The preference weights matching to each attribute level were summed for treatment profiles at the individual level. The summed preference weights of different treatment profiles were compared to determine which treatment profile would be most preferred.

The relative preference weights for each attribute level were also compared across the two subgroups: nmCRPC and mCRPC to determine whether preferences vary by patient disease status.

Further exploratory analysis was conducted to examine whether preferences vary by patient demographics, disease and medical history, as well as HRQoL using one-way analysis of

variance (ANOVA). For all analyses, p-values < 0.05 were considered statistically significant. Analyses were performed using R 3.5.1 [21] and SPSS 22.0 [22].

RESULTS

Participants

A total of 137 CRPC patients, recruited from 6 participating institutions and correctly answered the hold-out question, were included in the analyses, with 60 nmCRPC and 77 mCRPC. The mean age was 75.8 (SD=7.5), 83.9% were married, 45.3% had at least 2-year college education and 30.0% were still employed. Only 7 patients (5.1%) reported being currently cared for by a primary caregiver for their PC; 42.3% of patients suffered from hypertension. The details are shown in Supplementary table 1. Patients had been diagnosed with PC for an average of 6.8 years (SD=5.2) with 56 of them (40.9%) in Stage IV M1 (metastatic) at diagnosis. 7 patients (5.1%) had experienced symptomatic skeletal-related events (SSE) since diagnosis. None of the patients were diagnosed with having seizures or cognitive impairment at the time of enrolment in the study. The details are shown in Table 1.

Table 1. Physician-reported patient clinical characteristics.

		Total (N = 137)	
		N	%
Prostate cancer stage at diagnosis	Stage I	2	1.46%
	Stage IIA	14	10.22%
	Stage IIB	21	15.33%
	Stage III	28	20.44%
	Stage IV M0 (no evidence of metastasis)	13	9.49%
	Stage IV M1 (metastatic)	56	40.88%
	I do not have this information	3	2.19%
Experienced since prostate cancer diagnosis	SSE	7	5.11%
	Seizure	0	0.00%
	Cognitive impairment	0	0.00%
	Patient-reported fatigue	1	0.73%
	None of the above	129	94.16%
Metastatic status of prostate cancer	Yes	77	56.20%

	No	60	43.80%
ECOG grade at study enrolment	Grade 0	106	77.37%
	Grade 1	31	22.63%
Symptomatic status at study enrolment	Symptomatic	3	2.19%
	Asymptomatic	134	97.81%
Type of the first ADT received	LHRH analog, LHRH antagonist	86	62.77%
	Surgery (Orchiectomy)	7	5.11%
	Anti-androgen	86	62.77%
	Estrogen	1	0.73%
	Progesterone	0	0.00%
	Unknown	2	1.46%
Treatment currently prescribed for prostate cancer	Abiraterone	30	21.90%
	Enzalutamide	43	31.39%
	Anti-androgens	15	10.95%
	Androgen deprivation therapy	126	91.97%
	Strontium-89	0	0.00%
	Ra-233 (Xofigo)	1	0.73%
	External beam radiotherapy	3	2.19%
	Bisphosphonate	5	3.65%
	Denosumab	29	21.17%
	Opioid	1	0.73%
	Steroid	35	25.55%
	Non-steroidal anti-inflammatory medications / paracetamol / COX-2 inhibitors	4	2.92%
	Other (nmCRPC clinical trial participant)	4	2.92%
	Other (other prostate cancer clinical trial participant)	0	0.00%
	Other	11	8.03%
	No treatment / watch and wait	2	1.46%
Treatment prescribed prior to current treatment	Abiraterone	13	11.68%
	Enzalutamide	15	20.44%
	Anti-androgens	71	76.64%
	Androgen deprivation therapy	49	75.91%
	Strontium-89	1	0.73%
	Ra-233 (Xofigo)	13	9.49%
	External beam radiotherapy	34	25.55%
	Bisphosphonate	9	8.76%
	Denosumab	20	18.98%
	Surgery	11	
	Opioid	1	10.95%
	Steroid	10	0.73%
	Non-steroidal anti-inflammatory medications / paracetamol / COX-2 inhibitors	2	9.49%
	Other (nmCRPC clinical trial participant)	6	2.19%
	Other (other prostate cancer clinical trial participant)	4	4.38%
	Other	23	3.65%
	No other treatment other than first ADT	18	16.79%
	No treatment / watch and wait	0	0.00%
		Mean	**SD**

Duration of disease (years)	6.8	5.2
Duration of metastasis (months)	50.6	41.4
Duration of CRPC (months)	24.5	17.6

Abbreviations: ADT, androgen depletion therapy; CRPC, castrate-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; nmCRPC, non-metastatic CRPC.

Attributes and levels in the DCE

The final specific attributes included in the DCE were: i) risk of fatigue as a side-effect of treatment, ii) risk of falls or fractures as a side-effect of treatment, iii) risk of cognitive impairment as a side-effect of treatment, iv) risk of hypertension as a side-effect of treatment, v) extension of time until cancer-related pain occurs, and vi) risk of rashes as a side-effect of treatment (Supplementary table 2).

Patient preferences estimates

The hierarchical Bayesian logistic regression model results are reported in Figure 2 (and Supplementary table 3). All levels of all attributes were significantly associated with choice (all $p<0.05$). The greater the range of preference weights within an attribute, the stronger the relationship between that attribute and treatment choice.

Among the 137 CRPC patients, the "risk of cognitive impairment as a side-effect of treatment" was the most important attribute, with a relative importance (RI) of 27.47%, 95% CI: [24.80%, 30.14%]); followed by "extension of time until cancer-related pain occurs" (RI: 17.87%, 95% CI: [15.49%, 20.25%]), and the "risk of falls or fracture" (RI: 15.99%, CI: [14.73%, 17.25%]). The "risk of hypertension as a side-effect of treatment" (RI: 13.77%, CI: [12.73%, 14.81%]) had similar RI as "risk of rashes as a side-effect of treatment" (RI: 13.17%, CI: [12.15%, 14.19%]), followed by the "risk of fatigue as a side-effect of treatment" (RI: 11.74%, CI: [10.75%, 12.73%]) (Figure 3).

The RI for nmCRPC and mCRPC patients is further illustrated in Figure 4. Compared to mCRPC patients, nmCRPC patients placed more importance to risk of cognitive impairment as a side-effect of treatment (RI: 31.53% vs. 24.30%).

Based on the preference weights for attributes, summed preference weights were derived for three hypothetical treatment profiles with varying attribute levels in Table 2. Among CRPC patients, treatment profile I, with the lowest risk of side-effects, had significantly higher summed preference weights mean (mean [95% CI]: 3.23 [2.91, 3.56] vs. -2.09 [-2.30, -1.88] vs. -0.062 [-0.15, 0.026]), compared to the other two treatment profiles. The results were similar for both nmCRPC and mCRPC subgroups, in that majority of patients would prefer the profile with the lowest risk of side-effects.

Table 2. Summary of patient preference for different treatment profiles

		Treatment Profile I	Treatment Profile II	Treatment Profile III
Attribute levels	Risk of fatigue as a side-effect of treatment	15%	25%	35%
	Risk of falls or fracture as a side-effect of treatment	3%	20%	10%
	Risk of cognitive impairment as a side-effect of treatment	0%	5%	5%
	Risk of hypertension as a side-effect of treatment	5%	25%	15%
	Extension of time until cancer-related pain occurs	15 months	35 months	35 months
	Risk of rashes as a side-effect of treatment	5%	25%	15%
CRPC	Summed preference weights: Mean (95% CI)	3.234 (2.905, 3.563)	-2.088 (-2.296, -1.880)	-0.062 (-0.149, 0.026)
	Patients in favour of the profile: N (%)	128 (93.4%)	2 (1.5%)	7 (5.1%)
mCRPC	Summed preference weights: Mean (95% CI)	3.226 (2.776, 3.675)	-2.141 (-2.420, -1.861)	-0.151 (-0.268, -0.034)
	Patients in favour of the profile: N (%)	72 (93.5%)	1 (1.3%)	4 (5.2%)
nmCRPC	Summed preference weights: Mean (95% CI)	3.245 (2.758, 3.732)	-2.020 (-2.334, -1.706)	0.053 (-0.073, 0.179)
	Patients in favour of the profile: N (%)	56 (93.3%)	1 (1.7%)	3 (5.0%)

Abbreviations: CRPC, castrate-resistant prostate cancer; nmCRPC, non-metastatic CRPC.

Patient preferences by demographic, health history, and HRQoL

No significant differences in preferences weights were observed when comparing across demographic and health history variables (Supplementary table 4), nor was there any significant association between patient HRQoL and treatment preference (Supplementary table 5).

DISCUSSION

Dedicated qualitative interviews and DCEs play an important role in understanding and assessing patient's priorities in selecting available treatment options. DCEs have been used to elicit patient preferences in many other therapeutic fields as well as for prostate cancer [23–28]. This study also applied DCE methodology to determine the relative value that patients place on different attributes of their nmCRPC treatment. Our results suggest that CRPC patients (both nmCRPC and mCRPC) preferred safer treatment profiles with lesser risk of adverse events, given that most chose a hypothetical treatment profile with the least risk of side-effects. This is consistent with previous studies reporting that avoiding side-effects is relatively important to CRPC patients when considering treatment options [11,12]. In our study, CRPC patients considered the risk of cognitive impairment as a side-effect of treatment as the most important treatment attribute in nmCRPC, followed by extension of time until cancer-related pain occurs. Furthermore, patients were willing to trade-off effectiveness such as time until pain occurs for lower risk of side-effects such as cognitive impairment. Our results are also consistent with recent patient preference studies on CRPC treatment which reported cognition and memory problems as being relatively more important than other treatment attributes [12,29].

The impact on cognition and cognitive impairment in older adults with cancer has been reported, and it is thought that the triple conditions of aging, cancer and cancer treatment can

negatively affect cognition [30]. In prostate cancer, a meta-analysis by McGinty *et al*. showed that patients who received ADT performed significantly worse on visuomotor tasks compared to non-cancer control groups, and they noted that these findings are consistent with the known effects of testosterone on cognitive functioning in healthy men [31]. Any factor influencing cognition, therefore, is of great importance for the nmCRPC patients due to possibly relatively long period of ADT even prior to CRPC. Furthermore, in the nmCRPC state, patients are largely asymptomatic [32], and having cognitive impairment may greatly affect their ability to function independently, hence compromising their quality of life. Indeed, a study on Japanese community-dwelling older adults, showed that even mild cognitive impairment may be related to an increased risk for the development of disability in the future [33].

Looking at the degree of relative importance that mCRPC and nmCRPC patients separately placed on these two attributes, nmCRPC patients weighed more on risk of cognitive impairment while mCRPC patients weighed more on extension of time until cancer-related pain occurs. The difference in the degree of importance could be associated with most nmCRPC patients being asymptomatic, hence, accordingly, with a long duration of hormonal therapy, patients would want to spend their daily lives with a well-maintained QoL that precludes an increased risk of cognitive impairment while on treatment. As well, for mCRPC patients, due to increased age, the advanced stage of disease, and having experienced more bone metastasis-related pain, the importance of pain management to maintain QoL in the time they have left is understandable. In a qualitative study on pain in CRPC with bone metastasis, patients reported that bone pain was the most prominent and debilitating symptom associated with their condition, while another study found that bone pain was found to be the strongest predictor of skeletal related events, which are linked with a reduced quality of life and worse outcomes [34,35].

These results are, furthermore, congruent to a study by Nakayama *et al.,* which showed the differences in the patients' treatment preferences across different PC stages wherein patients with more advanced PC would prefer efficacy, whereas patients in less advanced PC would prefer maintenance of HRQoL[27]. Our study reflects a similar trend where the patients' preference reflects a mixture of putting more emphasis on efficacy (mCRPC) and on safety and tolerability (nmCRPC), with patients wanting to protect their QoL via an implied need to delay cognitive side-effects, as well as delaying cancer-related pain.

The need of Japanese patients for minimal side-effects while receiving effective nmCPRC therapy, as reflected in their preferences for safer treatment features, should be considered in treatment decision making. In Japan, new anti-androgens are available as nmCRPC treatments, with each treatment having its own reported central nervous system related features such as cognitive impairment and efficacy in delaying pain progression, among others. A better awareness of attributes that influence patients' treatment decision may enable clinicians to communicate with patients more effectively when making shared decisions on CRPC treatment strategies.

Finally, we attempted to put together the results here and from a physician preference study done in parallel with this study, and physicians were also asked about their preferences for the same set of attributes. From the physician perspective, "Extension of time until cancer-related pain occurs" were the most important, followed by "Risk of falls or fracture as a side effect of treatment". However, "Risk of cognitive impairment as a side effect of treatment" ranked only 4th in terms of attribute relative importance, showing a gap in how patients and physicians perceive treatment attributes in nmCRPC (Supplementary figure 1). Although no formal statistical comparison was conducted which warrants further investigation, the observed gap in patients' perception of nmCRPC treatment attributes versus that of physicians emphasizes the need for open communication of treatment benefits and risks between patients and their

physicians. In previous studies on gaps between patients and physicians' preferences in prostate cancer, different reasons for such gaps have been put forward, such as the structure of patient-physician encounters being typically physician-driven, or that physicians may judge patients' health using different reference points from their clinical practice experience [36,37]. Clinical decision making could be balanced by asking patients' regarding their personal preferences about treatment risks and benefits to establish patient-centered care.

A few limitations of this study should be noted. Due to sample selection during recruitment, respondents who were healthy enough to participate and were interested in research may be over-represented, hence could potentially introduce selection bias. Patient recruitment limited to the five institutions and the use of convenience sample may raise concerns about the external validity of the findings, however, descriptive data on the sample demographic and health characteristics reported would help put our sample within the context of the total CRPC population. In addition, responses in the DCE was towards hypothetical treatment profiles. One of the key aspects of this design was to stimulate possible clinical decisions, but this does not mean it has the same clinical meaning or emotional consequence of an actual decision. Hence, differences could arise between stated and actual response. Potential hypothetical bias can be limited by constructing choice questions that mimic realistic clinical choices as closely as possible and map clearly into clinical evidence. Although not central to the research questions, a few of our potential covariates (e.g., comorbidities) were reported directly from the patient without clinical verification. This decision was made to ease the burden on the physician investigators though it does introduce possible additional measurement error in the assessment of these variables. Lastly, the study failed to reach the target sample size of 150 patients and the sample sizes for the subgroups were limited in this study, caution should be taken in interpreting and generalizing the results in terms of subgroup comparisons.

CONCLUSION

Patients value safety and prioritize central nervous system related features such as lower risk of cognitive impairment and extension of time until pain occurs when choosing among nmCRPC treatment options with similar efficacy but different safety profiles. Such an assessment provides insights into the patients' nmCRPC treatment preferences and taking them into consideration will help physicians when developing their treatment strategies for their patients in Japan.

AUTHOR CONTRIBUTIONS

Hiroji Uemura contributed input to the study design as expert opinion leader, as well as to data collection and interpretation of the results. Hisashi Matsushima, Akira Yokomizo, Kazuki Kobayashi, Gaku Arai, and Takefumi Satoh were responsible for data collection and interpretation of study results. Vince Grillo, Shikha Singh and Yirong Chen were responsible for study design, data aggregation and analysis, study coordination, and medical writing. Dianne Athene Ledesma was responsible for creating the study design, data interpretation, and overall coordination of the study. All authors read and approved the final manuscript.

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COMPETING INTEREST

Dianne Athene Ledesma is an employee of Bayer Yakuhin, Ltd. Vince Grillo, Shikha Singh and Yirong Chen are employees of Kantar, Health Division.

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DATA AVAILABILITY

Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, time point and process of data access.

As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal.

Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

ETHICS STATEMENT

The protocol was approved by the respective Institutional Review Boards (IRBs) of each participating institution: Yokohama City University Ethical Committee (Approval No.

B181004003 for Yokohama City University Medical Center), Tokyo Metropolitan Hospital Clinical Research Evaluation Committee (Approval No. 19-a08 for Tokyo Metropolitan Hospital), Harasanshin Hospital Ethical Committee (Approval No. 2019-03 for Harasanshin Hospital), Dokkyo Medical University Saitama Medical Center Clinical Research Ethical Review Committee (Approval No. 1915 for Dokkyo Medical University Saitama Medical Center), Yokosuka Kyosai Hospital Clinical Research Ethical Review Committee (Approval No. 19-7 for Yokosuka Kyosai Hospital); and by a Central IRB (NPO Clinical Research Support Network Japan, Approval No. 20131) for Satoh Takefumi Prostate Clinic which did not have an in-house IRB.

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FIGURE LEGENDS

Figure 1. Example of preference-elicitation task.

Figure 2. Attribute-level preference weights: overall sample (N=137).

Figure 3. Relative importance of treatment attributes: overall sample (N=137).

Figure 4. Relative importance of treatment attributes: nmCRPC vs. mCRPC.

Figure 1. Example of preference-elicitation task.

30x34mm (500 x 500 DPI)

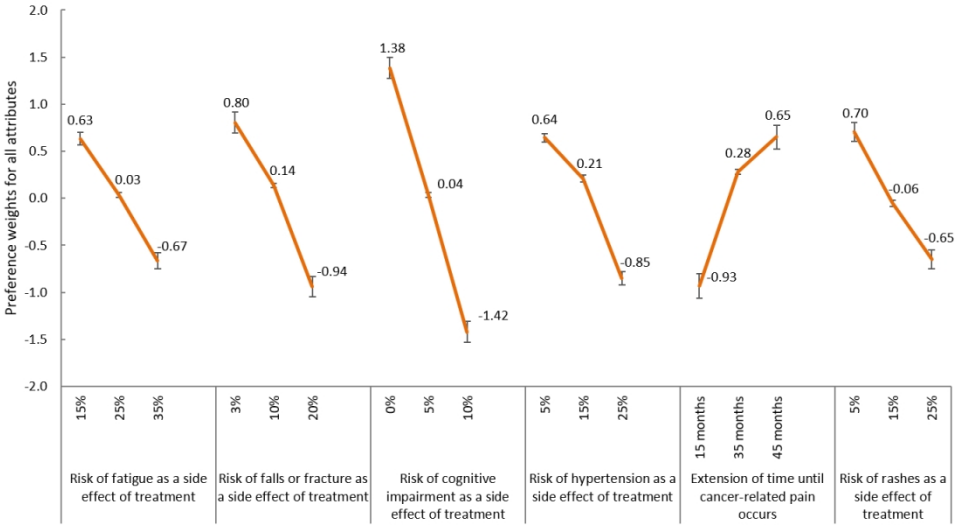


Figure 2. Attribute-level preference weights: overall sample (N=137).

72x39mm (500 x 500 DPI)

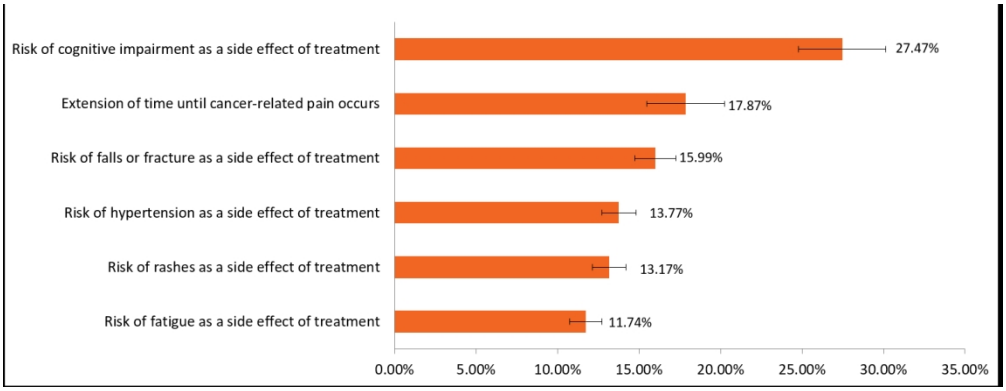


Figure 3. Relative importance of treatment attributes: overall sample (N=137).

80x30mm (500 x 500 DPI)

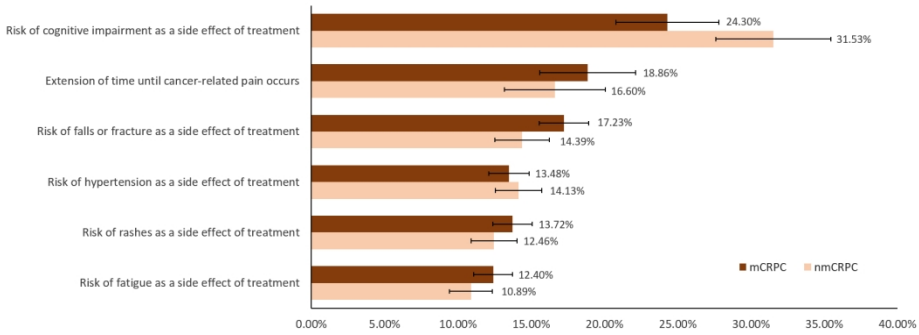
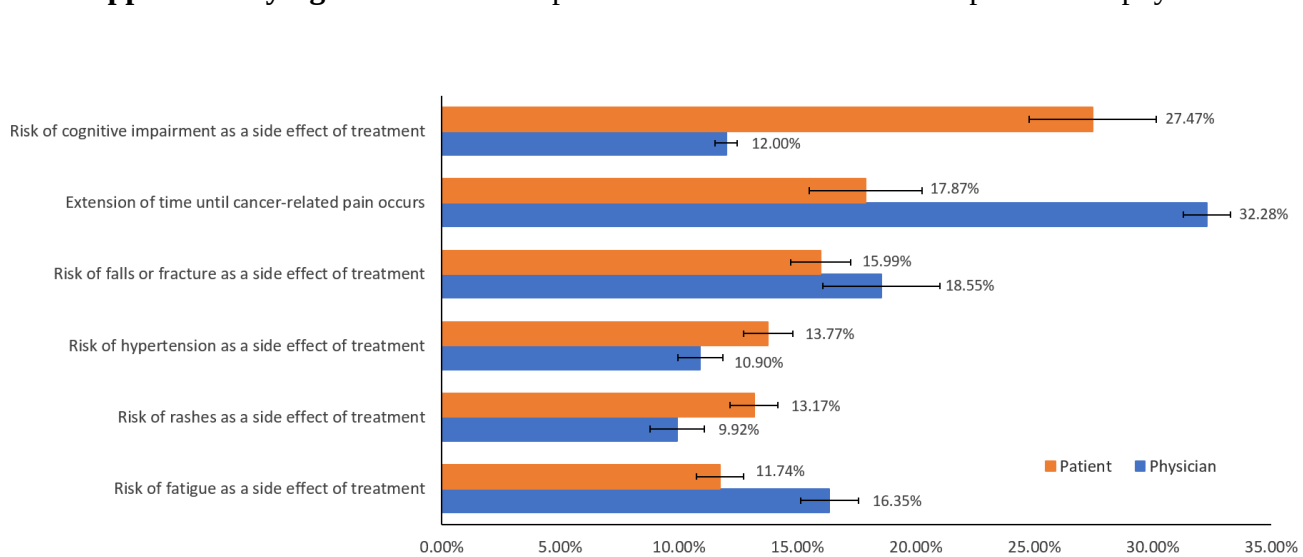


Figure 4. Relative importance of treatment attributes: nmCRPC vs. mCRPC.

100x35mm (500 x 500 DPI)

Supplementary material

Supplementary figure 1 Relative importance of treatment attributes: patients vs. physicians.



Supplementary table 1 Patient-reported demographics and other baseline characteristics.

		Total (N = 137)	
		N	%
Age [year] Category	<60	5	3.65%
	60-<70	20	14.60%
	70-<80	65	47.45%
	80-<90	43	31.39%
	≥90	3	2.19%
Marital status	Single	6	4.38%
	Married	115	83.94%
	Divorced	2	1.46%
	Separated	1	0.73%
	Widowed	10	7.30%
	Living with partner	2	1.46%
Level of education	Elementary school	0	0.00%
	Junior high school	23	16.79%
	High school	50	36.50%
	2-year college	4	2.92%
	4-year college	54	39.42%
	Graduate school	4	2.92%
	Decline to answer	1	0.73%
Employment status	Employed full-time	18	13.14%
	Self-employed	17	12.41%
	Part-time employed	6	4.38%
	Retired	62	45.26%
	Long-term disability	0	0.00%
	Short-term disability	0	0.00%
	Not employed (other than retired)	33	24.09%
Region of residence	Chubu	1	0.73%
	Kanto	105	76.64%
	Kyushu (including Okinawa)	30	21.90%
Household income	Less than ¥2,500,000	28	20.44%
	2,500,000 to ¥4,999,999	57	41.61%
	¥5,000,000 to ¥7,499,999	14	10.22%
	¥7,500,000 to ¥9,999,999	6	4.38%
	¥10,000,000 to ¥12,499,999	3	2.19%
	¥12,500,000 to ¥14,999,999	3	2.19%
	¥15,000,000 or more	2	1.46%
	Decline to answer	23	16.79%
Type of medical insurance	National health insurance	40	29.20%
	Late stage elderly insurance	76	55.47%
	Company/Social insurance	18	13.14%
	Welfare recipient	2	1.46%
	None of the above (all costs paid by myself/my family)	0	0.00%
Currently cared by a primary caregiver for prostate cancer	Yes	7	5.11%
	No	129	94.16%
Primary caregiver relationship	Wife	4	57.14%
	Child	1	14.29%

	Grandchild	0	0.00%
	Sibling	0	0.00%
	Other relative (parent, niece/nephew)	0	0.00%
	Hired professional caregiver	2	28.57%
	Other non-relative	0	0.00%
Physician-diagnosed comorbid condition	Cardiovascular disease	19	13.87%
	Chronic pulmonary disease	3	2.19%
	Rheumatologic disease	1	0.73%
	Peptic ulcer disease	16	11.68%
	Mild liver disease	13	9.49%
	Diabetes without chronic complications	16	11.68%
	Diabetes with chronic complications	5	3.65%
	Hemiplegia or paraplegia	1	0.73%
	Renal disease	4	2.92%
	Any malignancy, including leukemia and lymphoma	1	0.73%
	Moderate or severe liver disease	1	0.73%
	Other metastatic solid tumor currently being treated (other than that of the prostate)	1	0.73%
	AIDS/HIV	0	0.00%
	Hypertension	58	42.34%
	Prior malignancy, now in remission (malignancy other than that of the prostate)	10	7.30%
	None of the above	51	37.23%
		Mean	**SD**
Age		75.8	7.5

Supplementary table 2 List of attributes and levels in DCE

Attributes	Levels
i. Risk of fatigue as a side-effect of treatment	• 15% • 25% • 35%
ii. Risk of falls or fractures as a side-effect of treatment	• 3% • 10% • 20%
iii. Risk of cognitive impairment as a side-effect of treatment	• 0% • 5% • 10%
iv. Risk of hypertension as a side-effect of treatment	• 5% • 15% • 25%
v. Extension of time until cancer-related pain occurs	• 15 months • 35 months • 45 months
vi. Risk of rashes as a side-effect of treatment	• 5% • 15% • 25%

Supplementary table 3 Attribute-level preference weights: overall sample (N=137)

Attribute	Levels	Mean preference weight	SE	95% CI	p-value
Risk of fatigue as a side-effect of treatment	15%	0.633	0.035	0.564, 0.703	<0.001
	25%	0.034	0.013	0.009, 0.059	0.009
	35%	-0.667	0.043	-0.752, -0.582	<0.001
Risk of falls or fracture as a side- effect of treatment	3%	0.802	0.057	0.691, 0.913	<0.001
	10%	0.136	0.013	0.110, 0.161	<0.001
	20%	-0.938	0.054	-1.044, -0.831	<0.001
Risk of cognitive impairment as a side-effect of treatment	0%	1.385	0.058	1.271, 1.498	<0.001
	5%	0.035	0.012	0.012, 0.059	0.005
	10%	-1.420	0.056	-1.530, -1.310	<0.001
Risk of hypertension as a side-effect of treatment	5%	0.642	0.024	0.595, 0.689	<0.001
	15%	0.210	0.018	0.173, 0.246	<0.001
	25%	-0.852	0.037	-0.925, -0.779	<0.001
Extension of time until cancer-related pain occurs	15 months	-0.933	0.068	-1.066, -0.799	<0.001
	35 months	0.281	0.015	0.252, 0.309	<0.001
	45 months	0.652	0.064	0.526, 0.778	<0.001
Risk of rashes as a side-effect of treatment	5%	0.705	0.050	0.606, 0.803	<0.001
	15%	-0.056	0.016	-0.088, -0.024	<0.001
	25%	-0.648	0.051	-0.749, -0.548	<0.001

Supplementary table 4 Differences in preference weights across demographic and health history factors

			Risk of fatigue as a side-effect of treatment			Risk of falls or fracture as a side-effect of treatment			Risk of cognitive impairment as a side-effect of treatment			Risk of hypertension as a side-effect of treatment			Extension of time until cancer-related pain occurs			Risk of rashes as a side-effect of treatment		
		N	15%	25%	35%	3%	10%	20%	0%	5%	10%	5%	15%	25%	15 months	35 months	45 months	5%	15%	25%
Age group	<60	5	0.468	0.045	-0.513	0.429	0.123	-0.552	1.453	-0.083	-1.370	0.545	0.124	-0.794	-1.220	0.251	0.969	0.409	-0.093	-0.316
	60-<70	20	0.617	0.024	-0.641	0.755	0.170	-0.925	1.465	0.007	-1.472	0.646	0.174	-0.820	-1.015	0.274	0.741	0.728	-0.078	-0.651
	70-<80	65	0.620	0.021	-0.641	0.789	0.138	-0.927	1.362	0.055	-1.417	0.657	0.183	-0.840	-0.999	0.283	0.716	0.736	-0.037	-0.700
	≥80	46	0.691	0.059	-0.750	0.897	0.116	-1.013	1.353	0.031	-1.384	0.635	0.273	-0.908	-0.775	0.283	0.492	0.690	-0.074	-0.616
	p-value		0.621	0.602	0.595	0.455	0.621	0.479	0.922	0.119	0.966	0.849	0.096	0.745	0.380	0.978	0.297	0.683	0.689	0.548
Marital status	Married / Living with partner	117	0.646	0.034	-0.680	0.827	0.135	-0.961	1.373	0.043	-1.415	0.644	0.203	-0.847	-0.948	0.284	0.664	0.732	-0.060	-0.672
	Not	20	0.586	0.043	-0.629	0.686	0.135	-0.822	1.407	-0.012	-1.395	0.642	0.249	-0.891	-0.846	0.260	0.586	0.558	-0.040	-0.518
	p-value		0.558	0.797	0.687	0.394	0.980	0.377	0.837	0.113	0.902	0.975	0.396	0.744	0.608	0.568	0.679	0.234	0.681	0.303
Level of education	Completed university education	62	0.628	0.029	-0.657	0.785	0.141	-0.925	1.423	0.035	-1.457	0.625	0.219	-0.844	-0.899	0.290	0.609	0.699	-0.053	-0.646
	Not	75	0.647	0.040	-0.686	0.826	0.130	-0.956	1.339	0.035	-1.375	0.659	0.202	-0.862	-0.963	0.273	0.690	0.715	-0.061	-0.654
	p-value		0.790	0.677	0.733	0.721	0.681	0.784	0.476	0.970	0.467	0.487	0.656	0.802	0.640	0.566	0.532	0.879	0.821	0.939
Employment status	Employed	41	0.706	0.047	-0.753	0.879	0.149	-1.028	1.358	0.024	-1.382	0.667	0.228	-0.895	-0.994	0.279	0.714	0.740	-0.058	-0.682
	Not employed	96	0.609	0.030	-0.638	0.776	0.128	-0.905	1.386	0.040	-1.426	0.634	0.202	-0.836	-0.908	0.281	0.627	0.694	-0.057	-0.636
	p-value		0.211	0.533	0.228	0.409	0.476	0.301	0.824	0.555	0.723	0.532	0.531	0.456	0.569	0.945	0.536	0.675	0.989	0.685
Household income	Less than ¥5,000,000	85	0.644	0.037	-0.681	0.817	0.148	-0.965	1.413	0.038	-1.451	0.642	0.220	-0.862	-0.849	0.284	0.566	0.699	-0.051	-0.647
	¥5,000,000 to ¥9,999,999	20	0.660	0.062	-0.722	0.786	0.080	-0.866	1.263	0.019	-1.282	0.699	0.267	-0.966	-0.917	0.248	0.669	0.682	-0.040	-0.642
	¥10,000,000 or more	8	0.797	0.019	-0.816	1.191	0.090	-1.281	0.975	0.115	-1.090	0.669	0.150	-0.819	-1.453	0.398	1.055	0.864	-0.148	-0.717
	Decline to answer	24	0.540	0.010	-0.550	0.656	0.150	-0.807	1.486	0.010	-1.497	0.595	0.144	-0.738	-1.080	0.258	0.823	0.707	-0.063	-0.644
	p-value		0.468	0.701	0.533	0.274	0.253	0.297	0.237	0.297	0.335	0.677	0.227	0.353	0.164	0.177	0.206	0.893	0.571	0.991
Type of medical insurance	National health insurance	40	0.605	0.022	-0.627	0.746	0.137	-0.883	1.408	0.044	-1.452	0.628	0.196	-0.824	-0.989	0.272	0.718	0.685	-0.026	-0.659
	Late stage elderly insurance	76	0.677	0.040	-0.717	0.875	0.129	-1.004	1.348	0.047	-1.396	0.648	0.226	-0.874	-0.879	0.294	0.586	0.731	-0.070	-0.662
	Company/Social insurance	18	0.505	0.009	-0.513	0.587	0.163	-0.749	1.484	-0.029	-1.455	0.634	0.158	-0.793	-1.095	0.252	0.843	0.592	-0.067	-0.525
	Welfare recipient	2	1.017	0.342	-1.359	1.428	0.058	-1.486	0.904	-0.023	-0.880	0.894	0.343	-1.236	-0.445	0.225	0.221	1.292	-0.125	-1.167
	p-value		0.214	0.022	0.094	0.181	0.749	0.245	0.651	0.175	0.666	0.635	0.505	0.561	0.573	0.737	0.444	0.418	0.645	0.518
Currently cared by a primary caregiver for prostate cancer	Yes	7	0.665	0.058	-0.723	0.815	0.046	-0.861	1.137	0.071	-1.208	0.582	0.301	-0.883	-1.021	0.307	0.714	0.575	-0.062	-0.513
	No	129	0.636	0.034	-0.670	0.807	0.139	-0.946	1.390	0.033	-1.424	0.647	0.205	-0.852	-0.929	0.279	0.650	0.715	-0.057	-0.658
	p-value		0.858	0.678	0.789	0.975	0.116	0.731	0.334	0.480	0.398	0.551	0.254	0.805	0.769	0.681	0.827	0.542	0.944	0.536

Duration of prostate cancer (median split)	≤5 years	76	0.619	0.024	-0.643	0.808	0.135	-0.943	1.365	0.035	-1.401	0.635	0.197	-0.832	-0.994	0.295	0.699	0.700	-0.067	-0.633
	>5 years	60	0.662	0.049	-0.711	0.806	0.135	-0.941	1.393	0.035	-1.427	0.655	0.226	-0.882	-0.858	0.262	0.596	0.717	-0.045	-0.672
	p-value		0.553	0.337	0.443	0.984	0.990	0.986	0.815	0.969	0.815	0.676	0.427	0.538	0.327	0.270	0.431	0.867	0.511	0.709
ECOG grade at study enrolment	Grade 0	105	0.631	0.027	-0.658	0.811	0.135	-0.946	1.373	0.036	-1.409	0.639	0.205	-0.864	-0.973	0.282	0.690	0.719	-0.058	-0.661
	Grade 1	31	0.662	0.062	-0.724	0.796	0.132	-0.928	1.392	0.031	-1.423	0.661	0.227	-0.888	-0.802	0.275	0.527	0.669	-0.056	-0.613
	p-value		0.718	0.252	0.528	0.915	0.922	0.893	0.888	0.847	0.917	0.701	0.609	0.699	0.299	0.830	0.293	0.680	0.970	0.695
Symptomatic status at study enrolment	Symptomatic	3	0.853	-0.081	-0.772	0.979	0.097	-1.076	0.755	0.081	-0.836	0.547	0.124	-0.671	-1.990	0.252	1.739	1.039	-0.210	-0.829
	Asymptomatic	133	0.633	0.038	-0.671	0.803	0.136	-0.939	1.391	0.034	-1.425	0.646	0.212	-0.868	-0.910	0.281	0.629	0.700	-0.054	-0.646
	p-value		0.364	0.171	0.734	0.651	0.667	0.713	0.107	0.563	0.123	0.548	0.489	0.606	0.020	0.768	0.011	0.324	0.165	0.603

Supplementary table 5 Regression coefficients for preference weights and HRQoL sub-scale scores

		Risk of fatigue as a side-effect of treatment			Risk of falls or fracture as a side-effect of treatment			Risk of cognitive impairment as a side-effect of treatment			Risk of hypertension as a side-effect of treatment			Extension of time until cancer-related pain occurs			Risk of rashes as a side-effect of treatment		
	N	15%	25%	35%	3%	10%	20%	0%	5%	10%	5%	15%	25%	15 months	35 months	45 months	5%	15%	25%
Symptom scale: Urinary symptoms	137	0.002	0.000	-0.001	-0.001	0.001	0.000	0.003	0.000	-0.003	-0.001	0.002	0.001	0.004	-0.001	-0.004	-0.001	0.000	0.001
p-value		0.455	0.896	0.567	0.848	0.500	0.970	0.375	0.865	0.380	0.367	0.065	0.745	0.291	0.530	0.329	0.722	0.938	0.709
Symptom item: Incontinence aid	36	-0.004	-0.001	0.006	-0.007	-0.002	0.009	-0.001	-0.001	0.002	-0.004	-0.003	0.004	-0.005	0.000	0.005	-0.009	-0.001	0.010
p-value		0.022	0.052	0.012	0.020	0.103	0.003	0.741	0.148	0.519	0.011	0.545	0.060	0.249	0.596	0.247	0.002	0.524	0.002
Symptom scale: Bowel symptoms	137	-0.004	-0.001	0.004	-0.007	-0.001	0.009	0.004	-0.001	-0.003	-0.005	0.002	0.003	0.006	0.001	-0.007	-0.011	-0.001	0.012
p-value		0.256	0.603	0.280	0.144	0.217	0.068	0.428	0.564	0.487	0.020	0.233	0.368	0.303	0.366	0.195	0.013	0.370	0.006
Symptom scale: Hormonal treatment-related symptoms	137	0.004	0.000	-0.004	0.004	0.000	-0.003	-0.001	0.001	0.000	-0.002	0.000	0.002	0.001	0.003	-0.004	-0.002	0.000	0.002
p-value		0.148	0.908	0.224	0.422	0.725	0.451	0.894	0.472	0.988	0.315	0.834	0.486	0.800	0.036	0.460	0.608	0.908	0.590
Functional scales: Sexual activity	137	-0.002	0.000	0.003	-0.004	0.000	0.005	0.001	-0.003	0.002	-0.004	-0.003	0.007	-0.002	-0.001	0.003	-0.002	-0.002	0.004
p-value		0.587	0.852	0.619	0.546	0.843	0.498	0.850	0.054	0.835	0.227	0.131	0.127	0.830	0.734	0.761	0.716	0.367	0.519
Functional scales: Sexual functioning	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	17-18
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	12-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Unmet needs in non-metastatic castration-resistant prostate cancer from the Japanese patient perspective: a discrete choice experiment

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Title: Unmet needs in non-metastatic castration-resistant prostate cancer from the Japanese patient perspective: a discrete choice experiment

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ABSTRACT

Objectives With novel antiandrogen treatments of varying clinical benefits and risks becoming available, this study investigates how castration-resistant prostate cancer (CRPC) patients value differences in treatment characteristics.

Design Cross-sectional observational study.

Setting A discrete choice experiment was conducted. Patients chose between two hypothetical non-metastatic CRPC (nmCRPC) treatments defined by six attributes: Risk of fatigue, falls or fracture, cognitive impairment, hypertension, rashes as side-effects to treatment and extension of time until cancer-related pain occurs.

Participants A total of 137 adult male CRPC patients with no prior experience with chemotherapy and with ECOG status 0-1 were recruited. Patients were excluded if they participated in an investigational program outside of routine clinical practice, had a clinically relevant medical or psychiatric condition, or diagnosis of visceral/other metastases not related to the prostate, or were otherwise deemed ineligible by the referring physician.

Primary outcome measures Relative preference weights and relative importance of the attributes was estimated by Hierarchical Bayesian logistic regression.

Results Among the treatment attributes, "risk of cognitive impairment as a side-effect of treatment" was the most important attribute (relative importance (RI) [95% confidence interval]: 27.47% [24.80%, 30.14%]), followed by "extension of time until cancer-related pain occurs" (RI: 17.87% [15.49%, 20.25%]), and the "risk of falls or fracture" (RI: 15.99% [14.73%, 17.25%]). The "risk of hypertension as a side-effect of treatment" (RI: 13.77% [12.73%, 14.81%]) had similar RI as "risk of rashes as a side-effect of treatment" (RI: 13.17% [12.15%, 14.19%]), followed by the "risk of fatigue as a side-effect of treatment" (RI: 11.74% [10.75%, 12.73%]).

Conclusions Patients consider the risk of cognitive impairment as a side-effect of treatment as the most important attribute in nmCRPC, followed by the extension of time until pain occurs, and the risk of falls and fracture. These features should be considered in treatment decision-making for nmCRPC in Japan.

STRENGTHS AND LIMITATIONS

- A major strength of this study is the application of the DCE methodology to determine the relative value that patients place on different attributes of their nmCRPC treatment.
- Another strength lies in the development of the final DCE survey, which encompassed a series of systematic steps including literature review, qualitative exploratory interviews, and cognitive interviews with CRPC patients.
- A limitation is the representativeness of the CRPC patients included in this study, who were a convenient sample recruited from a few selected facilities in Japan.
- Another limitation is that the DCE design may not have the same clinical meaning or emotional consequence of an actual treatment decision.

INTRODUCTION

Castration-resistant prostate cancer (CRPC), defined as rising prostate-specific antigen (PSA) levels despite castrate levels of testosterone and ongoing androgen deprivation therapy (ADT), represents 10-20% of prostate cancer (PC) patients [1]. One-third of CRPC patients progress to bone metastasis within two years. Bone metastases can cause significant pain and skeletal-related events and increase the risk of mortality, hence there is a need to delay or prevent progression to the metastatic state for non-metastatic CRPC (nmCRPC) patients and possibly prolong overall survival (OS) while maintaining the patient's quality of life [2].

Treatment options for nmCRPC traditionally include ADT in the form of luteinizing hormone-releasing hormone (LHRH) and first-generation nonsteroidal antiandrogens (flutamide, bicalutamide), as well as novel hormones enzalutamide and abiraterone acetate (approved CRPC treatments in Japan). The recent approval of second-generation androgen receptor inhibitors apalutamide and darolutamide as new treatment options for nmCRPC in Japan could affect the treatment landscape.

Enzalutamide and apalutamide reported extension of metastasis-free survival (MFS) (36.6 months enzalutamide vs. 14.7 months placebo; 40.5 months apalutamide vs. 16.2 months placebo) in the primary analyses of their respective clinical trials in nmCRPC, and reported efficacy in extending overall survival (67.0 months for enzalutamide vs. 56.3 months placebo; 73.9 months for apalutamide vs. 59.9 months placebo), based on final analyses [3–6]. They also reported adverse effects during treatment such as fatigue (enzalutamide: 46%; apalutamide: 33%, all grades), falls (enzalutamide: 18%; apalutamide: 22%), and seizures (enzalutamide: <1%; apalutamide: 0.2%, in subjects which excluded previous history of seizures) [3,4,6]. More recently, darolutamide demonstrated extension of MFS (40.4 months vs. 18.4 months placebo) with rates of adverse events reported as falls (5.2%), fatigue (13.2%), rash (3.1%) and seizures (0.2% in subjects that included patients with previous history of

seizures), and extension of overall survival (31% reduction in death compared to placebo; hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.53-0.88; two-sided P=0.003) [7].

With these novel antiandrogen treatments of different clinical benefits and risks becoming available, it is important to understand how CRPC patients value differences in treatment characteristics. Patients' health-related preferences simply go beyond cure and are particularly cogent in situations in which several choices of optimal therapy are available and treatment decisions have to be made [8]. This is underlined by a study in Japan which reported that prostate cancer patients preferred shared decision making with physicians and were interested to be involved in the decision making on their disease management [9]. Overall, increased patient involvement is an important part of quality improvement since it has been associated with improved health outcomes [10].

Previous studies elucidating patient preferences in CRPC treatment revealed that patients valued attributes affecting their daily quality of life (such as treatment side-effects or bone pain) over extension of survival [11–15]. However, most of these studies were related to metastatic CRPC treatment, with limited information on patient preferences towards nmCRPC treatment. Therefore, this study aimed to investigate how Japanese CPRC patients would value the differences in the attributes of treatment options in nmCRPC.

METHODS

Study design

A discrete choice experiment (DCE) was conducted to measure nmCRPC patient's treatment preferences in Japan. It was conducted in three phases i) phase 1, the concept elicitation phase, to elicit concepts for the development of attributes list for DCE, ii) phase 2, cognitive pre-testing phase, to solicit feedback and determine the content validity of the draft DCE

questionnaire, and iii) phase 3, final DCE paper-based survey. Survey development took place in accordance with good research practices [16]. The protocol was approved by the respective Institutional Review Boards (IRBs) of each participating institution: Yokohama City University Ethical Committee (Approval No. B181004003 for Yokohama City University Medical Center), Tokyo Metropolitan Hospital Clinical Research Evaluation Committee (Approval No. 19-a08 for Tokyo Metropolitan Hospital), Harasanshin Hospital Ethical Committee (Approval No. 2019-03 for Harasanshin Hospital), Dokkyo Medical University Saitama Medical Center Clinical Research Ethical Review Committee (Approval No. 1915 for Dokkyo Medical University Saitama Medical Center), Yokosuka Kyosai Hospital Clinical Research Ethical Review Committee (Approval No. 19-7 for Yokosuka Kyosai Hospital); and by a Central IRB (NPO Clinical Research Support Network Japan, Approval No. 20131) for Satoh Takefumi Prostate Clinic which did not have an in-house IRB. The participating institutions were selected to ensure representativeness in terms of geographic distribution in Japan. Informed consent was obtained from all the participants prior to any activities related to the study.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. Part of the data used in this study were obtained from patients who provided self-reported information through the survey.

Study population

Patients recruited in all phases of this study fulfilled the following inclusion criteria: i) aged 20 and above, ii) male, diagnosed with either non-metastatic or metastatic CRPC, iii) no prior experience with chemotherapy, iv) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1, and v) able to read and understand Japanese, and can provide

informed consent and complete the survey instrument. Patients were excluded if they were participating in an investigational program with interventions outside of routine clinical practice, had a clinically-relevant medical or psychiatric condition which, in the opinion of the investigator would interfere with completing the study, a diagnosis of visceral metastasis/other metastasis not related to the prostate, or were otherwise deemed ineligible by the referring physician. Patients recruited in the qualitative phases (phase 1 and 2) were excluded as participants for the main DCE survey. For the quantitative phase, a consecutive, convenience sample of patients were recruited from each participating institution, to account for potential variations in treatment patterns, scheduling of hospital visits, and the size and general health of the population of interest.

A target sample size of 150 patients was planned to complete the main DCE survey. Each respondent would answer ten preference-elicitation questions choosing between two hypothetical treatments defined by six attributes, which followed the common guidelines and rule-of-thumb for the sample size in DCE studies [17], similar to majority of previously published studies [16]. The sample size fulfilled the recommendation of maximum standard error of 0.05 [18] based on simulation and was deemed feasible to recruit in Japan.

Survey development

Survey development encompassed a series of systematic steps including literature review, qualitative exploratory interviews and cognitive interviews with CRPC patients (nmCPRC and mCRPC patients). Literature review was conducted to identify and characterize relevant treatment attributes for nmCRPC treatments using Pubmed and Embase. Attributes relating to impact on health-related quality of life (HRQoL) and efficacy were identified. Qualitative face-to-face, 60-minute interviews were conducted in the concept elicitation phase with four nmCRPC and four mCRPC patients. Findings from this phase together with literature review

were used to elicit concepts and attributes for inclusion in the draft DCE survey. The draft survey was tested in cognitive face-to-face interviews on another group of patients (four nmCRPC and four mCRPC patients), and feedback from the interviews were used to finalize the DCE survey.

DCE survey

The DCE task included a series of preference-elicitation questions, each asking respondents to choose between hypothetical treatments for nmCRPC. An example of a single preference-elicitation question presented to respondents is shown in Figure 1.

The DCE was designed to collect data to estimate relative preference weights, relative importance of the attributes, and the trade-offs patients were willing to make in one attribute for changes in another attribute. In addition to the DCE choice tasks, demographic and clinical patient characteristics, as well as HRQoL measurement (EORTC QLQ-PR25) [19] were collected from patients. Patients' prostate cancer related clinical characteristics and screening information were reported by the physicians. The experimental design of the DCE was a balanced overlap design using Sawtooth Software (Lighthouse Studio, v9.5.3) targeting only the main effect of the attributes. This method guaranteed that sufficient patients saw different combinations of attributes and levels, with all attribute levels varying independently according to the experimental design. The design of the DCE in this study featured eight blocks of ten preference-elicitation questions and each patient was given one block of questions. In addition, each patient was also given a hold-out question containing two treatment profiles with the absolute best-case scenario and the absolute worst-case scenario to assess and assure comprehension of the DCE.

Statistical analysis

The study sample was described with respect to demographics, disease history, comorbidity and HRQoL variables using frequencies and percentages for categorical variables and counts, means and standard deviations (SDs) for continuous variables.

The choice data was analyzed using hierarchical Bayesian logistic regression models with effects coding parameterization (the third level being the base level) and non-informative priors for the parameters, using *rjags* package in R [20]. The outcome variable of this model was choice, and the predictor variables were the levels within each attribute. Point estimates of model coefficients represent mean preference weights at the aggregate level, defined as the marginal utility of a change in that attribute. With these estimates, the magnitude of the trade-offs for patients choosing among the attribute levels can be assessed. The relative importance estimates were calculated at the respondent level by dividing the range of each attribute (utility of most favorable level minus utility of least favorable level) by the sum of the ranges of all attributes. The resulting estimates are percentages, reflecting the importance of each attribute relative to the others.

The preference weights matching to each attribute level were summed for treatment profiles at the individual level. The summed preference weights of different treatment profiles were compared to determine which treatment profile would be most preferred.

The relative preference weights for each attribute level were also compared across two subgroups: nmCRPC and mCRPC, to determine whether preferences vary by patient disease status.

Further exploratory analysis was conducted to examine whether preferences vary by patient demographics, disease and medical history, as well as HRQoL using one-way analysis of

variance (ANOVA). For all analyses, p-values < 0.05 were considered statistically significant. Analyses were performed using R 3.5.1 [21] and SPSS 22.0 [22].

RESULTS

Participants

A total of 137 CRPC patients, recruited from 6 participating institutions and correctly answered the hold-out question, were included in the analyses, with 60 nmCRPC and 77 mCRPC. The mean age was 75.8 (SD=7.5), 83.9% were married, 45.3% had at least 2-year college education and 30.0% were still employed. Only 7 patients (5.1%) reported being currently cared for by a primary caregiver for their PC; 42.3% of patients suffered from hypertension. The details are shown in Supplementary table 1. Patients had been diagnosed with PC for an average of 6.8 years (SD=5.2) with 56 of them (40.9%) in Stage IV M1 (metastatic) at diagnosis. 7 patients (5.1%) had experienced symptomatic skeletal-related events (SSE) since diagnosis. None of the patients were diagnosed with having seizures or cognitive impairment at the time of enrolment in the study. The details are shown in Table 1.

Table 1. Physician-reported patient clinical characteristics.

		Total (N = 137)	
		N	%
Prostate cancer stage at diagnosis	Stage I	2	1.46%
	Stage IIA	14	10.22%
	Stage IIB	21	15.33%
	Stage III	28	20.44%
	Stage IV M0 (no evidence of metastasis)	13	9.49%
	Stage IV M1 (metastatic)	56	40.88%
	I do not have this information	3	2.19%
Experienced since prostate cancer diagnosis	Symptomatic skeletal-related events (SSE)	7	5.11%
	Seizure	0	0.00%
	Cognitive impairment	0	0.00%
	Patient-reported fatigue	1	0.73%
	None of the above	129	94.16%
Metastatic status of prostate cancer	Yes	77	56.20%

	No	60	43.80%
ECOG grade at study enrolment	Grade 0	106	77.37%
	Grade 1	31	22.63%
Symptomatic status at study enrolment	Symptomatic	3	2.19%
	Asymptomatic	134	97.81%
Type of the first ADT received	LHRH agonist, LHRH antagonist	86	62.77%
	Surgery (Orchiectomy)	7	5.11%
	Antiandrogen	86	62.77%
	Estrogen	1	0.73%
	Unknown	2	1.46%
Treatment currently prescribed for prostate cancer	Abiraterone	30	21.90%
	Enzalutamide	43	31.39%
	Antiandrogen	15	10.95%
	LHRH agonist, LHRH antagonist	126	91.97%
	Ra-233 (Xofigo)	1	0.73%
	External beam radiotherapy (EBRT)	3	2.19%
	Bisphosphonate	5	3.65%
	Denosumab	29	21.17%
	Opioid	1	0.73%
	Steroid	35	25.55%
	NSAID / paracetamol / COX-2 inhibitors	4	2.92%
	Other	11	8.03%
	No treatment / watch and wait	2	1.46%
Treatment prescribed prior to current treatment	Abiraterone	13	11.68%
	Enzalutamide	15	20.44%
	Antiandrogen	71	76.64%
	LHRH agonist, LHRH antagonist	49	75.91%
	Strontium-89	1	0.73%
	Ra-233 (Xofigo)	13	9.49%
	External beam radiotherapy (EBRT)	34	25.55%
	Bisphosphonate	9	8.76%
	Denosumab	20	18.98%
	Surgery	11	
	Opioid	1	10.95%
	Steroid	10	0.73%
	NSAID / paracetamol / COX-2 inhibitors	2	9.49%
	Other (nmCRPC clinical trial participant)	6	2.19%
	Other (other prostate cancer clinical trial participant)	4	4.38%
	Other	23	3.65%
	No other treatment other than first ADT	18	16.79%
		Mean	**SD**
Duration of disease (years)		6.8	5.2
Duration of metastasis (months)		50.6	41.4
Duration of CRPC (months)		24.5	17.6

Abbreviations: ADT, androgen depletion therapy; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; LHRH, luteinizing hormone-releasing hormone; nmCRPC, non-metastatic CRPC; NSAID, non-steroidal anti-inflammatory medicine.

Attributes and levels in the DCE

The final specific attributes included in the DCE were: i) risk of fatigue as a side-effect of treatment, ii) risk of falls or fractures as a side-effect of treatment, iii) risk of cognitive impairment as a side-effect of treatment, iv) risk of hypertension as a side-effect of treatment, v) extension of time until cancer-related pain occurs, and vi) risk of rashes as a side-effect of treatment (Supplementary table 2).

Patient preferences estimates

The hierarchical Bayesian logistic regression model results are reported in Figure 2 (and Supplementary table 3). All levels of all attributes were significantly associated with choice (all $p<0.05$). The greater the range of preference weights within an attribute, the stronger the relationship between that attribute and treatment choice.

Among the 137 CRPC patients, the "risk of cognitive impairment as a side-effect of treatment" was the most important attribute, with a relative importance (RI) of 27.47%, 95% CI: [24.80%, 30.14%]); followed by "extension of time until cancer-related pain occurs" (RI: 17.87%, 95% CI: [15.49%, 20.25%]), and the "risk of falls or fracture" (RI: 15.99%, CI: [14.73%, 17.25%]). The "risk of hypertension as a side-effect of treatment" (RI: 13.77%, CI: [12.73%, 14.81%]) had similar RI as "risk of rashes as a side-effect of treatment" (RI: 13.17%, CI: [12.15%, 14.19%]), followed by the "risk of fatigue as a side-effect of treatment" (RI: 11.74%, CI: [10.75%, 12.73%]) (Figure 3).

The RI for nmCRPC and mCRPC patients is further illustrated in Figure 4. Compared to mCRPC patients, nmCRPC patients placed more importance to risk of cognitive impairment as a side-effect of treatment (RI: 31.53% vs. 24.30%).

Based on the preference weights for attributes, summed preference weights were derived for three hypothetical treatment profiles with varying attribute levels in Table 2. Among CRPC patients, treatment profile I, with the lowest risk of side-effects, had significantly higher summed preference weights mean (mean [95% CI]: 3.23 [2.91, 3.56] vs. -2.09 [-2.30, -1.88] vs. -0.062 [-0.15, 0.026]), compared to the other two treatment profiles. The results were similar for both nmCRPC and mCRPC subgroups, in that majority of patients would prefer the profile with the lowest risk of side-effects.

Table 2. Summary of patient preference for different treatment profiles

		Treatment Profile I	Treatment Profile II	Treatment Profile III
Attribute levels	Risk of fatigue as a side-effect of treatment	15%	25%	35%
	Risk of falls or fracture as a side-effect of treatment	3%	20%	10%
	Risk of cognitive impairment as a side-effect of treatment	0%	5%	5%
	Risk of hypertension as a side-effect of treatment	5%	25%	15%
	Extension of time until cancer-related pain occurs	15 months	35 months	35 months
	Risk of rashes as a side-effect of treatment	5%	25%	15%
CRPC	Summed preference weights: Mean (95% CI)	3.234 (2.905, 3.563)	-2.088 (-2.296, -1.880)	-0.062 (-0.149, 0.026)
	Patients in favour of the profile: N (%)	128 (93.4%)	2 (1.5%)	7 (5.1%)
mCRPC	Summed preference weights: Mean (95% CI)	3.226 (2.776, 3.675)	-2.141 (-2.420, -1.861)	-0.151 (-0.268, -0.034)
	Patients in favour of the profile: N (%)	72 (93.5%)	1 (1.3%)	4 (5.2%)
nmCRPC	Summed preference weights: Mean (95% CI)	3.245 (2.758, 3.732)	-2.020 (-2.334, -1.706)	0.053 (-0.073, 0.179)
	Patients in favour of the profile: N (%)	56 (93.3%)	1 (1.7%)	3 (5.0%)

Abbreviations: CRPC, castration-resistant prostate cancer; nmCRPC, non-metastatic CRPC.

Patient preferences by demographic, health history, and HRQoL

No significant differences in preferences weights were observed when comparing across demographic and health history variables (Supplementary table 4), nor was there any significant association between patient HRQoL and treatment preference (Supplementary table 5).

DISCUSSION

Dedicated qualitative interviews and DCEs play an important role in understanding and assessing patient's priorities in selecting available treatment options. DCEs have been used to elicit patient preferences in many other therapeutic fields as well as for prostate cancer [23–28]. This study also applied DCE methodology to determine the relative value that patients place on different attributes of their nmCRPC treatment. Our results suggest that CRPC patients (both nmCRPC and mCRPC) preferred safer treatment profiles with lesser risk of adverse events, given that most chose a hypothetical treatment profile with the least risk of side-effects. This is consistent with previous studies reporting that avoiding side-effects is relatively important to CRPC patients when considering treatment options [11,12]. In our study, CRPC patients considered the risk of cognitive impairment as a side-effect of treatment as the most important treatment attribute in nmCRPC, followed by extension of time until cancer-related pain occurs. Furthermore, patients were willing to trade-off effectiveness such as time until pain occurs for lower risk of side-effects such as cognitive impairment. Our results are also consistent with recent patient preference studies on CRPC treatment which reported cognition and memory problems as being relatively more important than other treatment attributes [12,29].

The impact on cognition and cognitive impairment in older adults with cancer has been reported, and it is thought that the triple conditions of aging, cancer and cancer treatment can negatively affect cognition [30]. In prostate cancer, a meta-analysis by McGinty *et al*. showed that patients who received ADT performed significantly worse on visuomotor tasks compared to non-cancer control groups, and they noted that these findings are consistent with the known effects of testosterone on cognitive functioning in healthy men [31]. Any factor influencing cognition, therefore, is of great importance for nmCRPC patients due to the possibly relatively

long period of ADT treatment even prior to CRPC. Furthermore, in the nmCRPC state, patients are largely asymptomatic [32], and having cognitive impairment may greatly affect their ability to function independently, hence compromising their quality of life. Indeed, a study on Japanese community-dwelling older adults showed that even mild cognitive impairment may be related to an increased risk for the development of disability in the future [33].

Looking at the degree of relative importance that mCRPC and nmCRPC patients separately placed on these two attributes, nmCRPC patients weighed more on risk of cognitive impairment while mCRPC patients weighed more on extension of time until cancer-related pain occurs. The difference in the degree of importance could be associated with most nmCRPC patients being asymptomatic, hence, accordingly, with a long duration of hormonal therapy, patients would want to spend their daily lives with a well-maintained HRQoL that precludes an increased risk of cognitive impairment while on treatment. Similarly, for mCRPC patients, due to increased age, advanced disease stage, and having experienced more bone metastasis-related pain, the importance of pain management to maintain HRQoL in the time they have left is understandable. In a qualitative study on pain in CRPC with bone metastasis, patients reported that bone pain was the most prominent and debilitating symptom associated with their condition, while another study found that bone pain was found to be the strongest predictor of skeletal related events, which are linked with a reduced quality of life and worse outcomes [34,35].

These results are also congruent to a study by Nakayama *et al.,* which showed the differences in the patients' treatment preferences across different PC stages wherein patients with more advanced PC would prefer efficacy, whereas patients in less advanced PC would prefer maintenance of HRQoL [27]. Our study reflects a similar trend where the patients' preference reflected a mixture of putting more emphasis on efficacy (mCRPC) as well as on safety and

tolerability (nmCRPC), with patients wanting to protect their HRQoL via an implied need to delay cognitive side-effects, as well as delaying cancer-related pain.

The need of Japanese patients for minimal side-effects while receiving effective nmCPRC therapy, as reflected in their preferences for safer treatment features, should be considered in treatment decision making. Novel antiandrogen treatments have their own reported central nervous system related treatment features relating to cognitive impairment and efficacy in delaying pain progression, among others. A better awareness of attributes that influence patients' treatment decision may enable clinicians to communicate with patients more effectively when making shared decisions on CRPC treatment strategies.

Finally, we attempted to put together the results here and from a physician preference study done in parallel with this study, and physicians were also asked about their preferences for the same set of attributes. From the physician perspective, "Extension of time until cancer-related pain occurs" were the most important, followed by "Risk of falls or fracture as a side effect of treatment". However, "Risk of cognitive impairment as a side effect of treatment" ranked only 4th in terms of attribute relative importance, showing a gap in how patients and physicians perceive treatment attributes in nmCRPC (Supplementary figure 1). Although no formal statistical comparison was conducted, the observed gap in patients' and physicians' perception of nmCRPC treatment attributes emphasizes the need for open communication of treatment benefits and risks between patients and their physicians. In previous studies on gaps between patients and physicians' preferences in prostate cancer, different reasons for such gaps have been put forward, such as the structure of patient-physician encounters being typically physician-driven, or that physicians may judge patients' health using different reference points from their clinical practice experience [36,37]. Clinical decision making could be balanced by asking patients' regarding their personal preferences about treatment risks and benefits to establish patient-centered care.

A few limitations of this study should be noted. Due to sample selection during recruitment, respondents who were healthy enough to participate and were interested in research may be over-represented, hence could potentially introduce selection bias. Patient recruitment limited to the five institutions and the use of convenience sample may raise concerns about the external validity of the findings, however, descriptive data on the sample demographic and health characteristics reported would help put our sample within the context of the total CRPC population. In addition, responses in the DCE were centered around hypothetical treatment profiles. One of the key aspects of this design was to stimulate possible clinical decisions, but this does not mean it has the same clinical meaning or emotional consequence of an actual decision. Hence, differences could arise between stated and actual response. Potential hypothetical bias can be limited by constructing choice questions that mimic realistic clinical choices as closely as possible and map clearly into clinical evidence. Although not central to the research questions, a few of our potential covariates (e.g., comorbidities) were reported directly from the patient without clinical verification. This decision was made to ease the burden on the physician investigators though it does introduce possible additional measurement error in the assessment of these variables. Lastly, the study failed to reach the target sample size of 150 patients and the sample sizes for the subgroups were limited in this study, therefore, caution should be taken in interpreting and generalizing the results in terms of subgroup comparisons.

CONCLUSION

Patients value safety and prioritize features such as lower risk of cognitive impairment, and extension of time until pain occurs when choosing among nmCRPC treatment options with similar efficacy but different safety profiles. Such an assessment provides insights into the

patients' nmCRPC treatment preferences and taking them into consideration will help physicians when developing their treatment strategies for their patients in Japan.

AUTHOR CONTRIBUTIONS

Hiroji Uemura contributed input to the study design as expert opinion leader, as well as to data collection and interpretation of the results. Hisashi Matsushima, Akira Yokomizo, Kazuki Kobayashi, Gaku Arai, and Takefumi Satoh were responsible for data collection and interpretation of study results. Vince Grillo, Shikha Singh and Yirong Chen were responsible for study design, data aggregation and analysis, study coordination, and medical writing. Dianne Athene Ledesma was responsible for creating the study design, data interpretation, and overall coordination of the study. All authors read and approved the final manuscript.

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COMPETING INTEREST

Dianne Athene Ledesma is an employee of Bayer Yakuhin, Ltd. Vince Grillo, Shikha Singh and Yirong Chen are employees of Kantar, Health Division.

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DATA AVAILABILITY

Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, time point and process of data access.

As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal.

Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

ETHICS STATEMENT

The protocol was approved by the respective Institutional Review Boards (IRBs) of each participating institution: Yokohama City University Ethical Committee (Approval No.

B181004003 for Yokohama City University Medical Center), Tokyo Metropolitan Hospital Clinical Research Evaluation Committee (Approval No. 19-a08 for Tokyo Metropolitan Hospital), Harasanshin Hospital Ethical Committee (Approval No. 2019-03 for Harasanshin Hospital), Dokkyo Medical University Saitama Medical Center Clinical Research Ethical Review Committee (Approval No. 1915 for Dokkyo Medical University Saitama Medical Center), Yokosuka Kyosai Hospital Clinical Research Ethical Review Committee (Approval No. 19-7 for Yokosuka Kyosai Hospital); and by a Central IRB (NPO Clinical Research Support Network Japan, Approval No. 20131) for Satoh Takefumi Prostate Clinic which did not have an in-house IRB.

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FIGURE LEGENDS

Figure 1. Example of preference-elicitation task.

Figure 2. Attribute-level preference weights: overall sample (N=137).

Figure 3. Relative importance of treatment attributes: overall sample (N=137).

Figure 4. Relative importance of treatment attributes: nmCRPC vs. mCRPC.

Figure 1. Example of preference-elicitation task.

30x34mm (500 x 500 DPI)

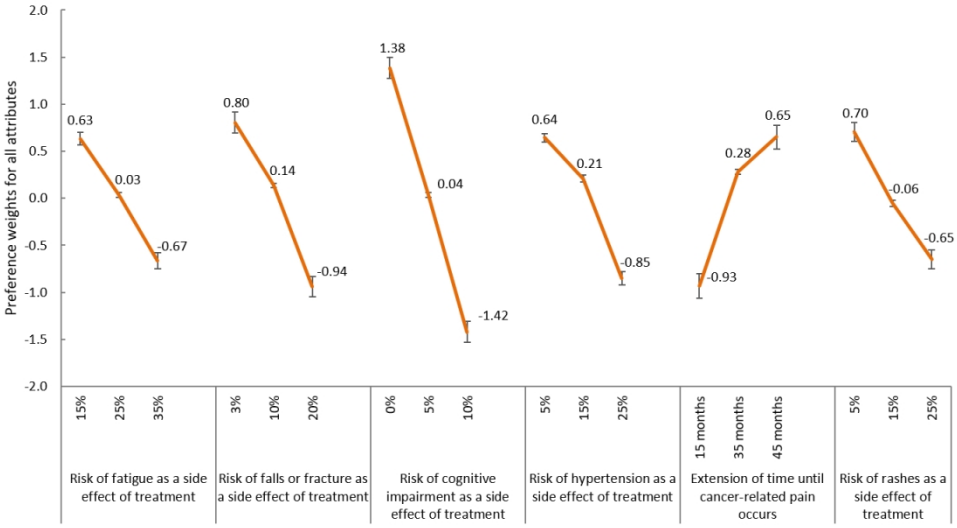


Figure 2. Attribute-level preference weights: overall sample (N=137).

72x39mm (500 x 500 DPI)

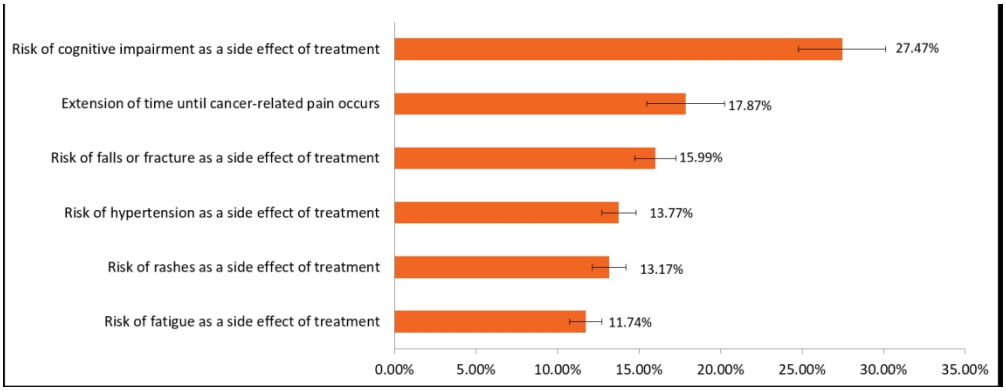


Figure 3. Relative importance of treatment attributes: overall sample (N=137).

80x30mm (500 x 500 DPI)

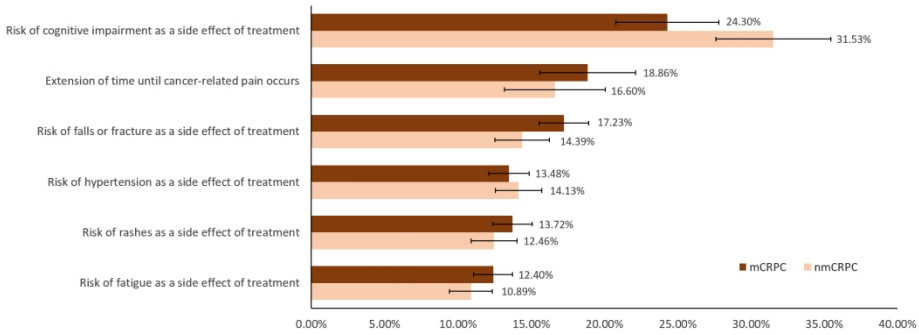
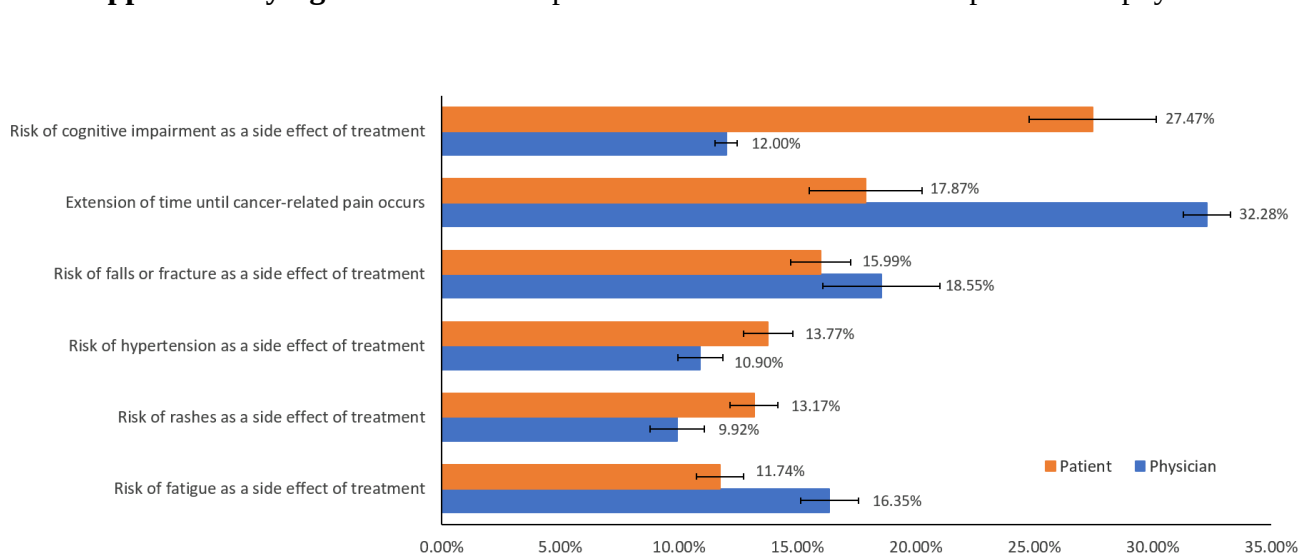


Figure 4. Relative importance of treatment attributes: nmCRPC vs. mCRPC.

100x35mm (500 x 500 DPI)

Supplementary material

Supplementary figure 1 Relative importance of treatment attributes: patients vs. physicians.



Supplementary table 1 Patient-reported demographics and other baseline characteristics.

		Total (N = 137)	
		N	%
Age [year] Category	<60	5	3.65%
	60-<70	20	14.60%
	70-<80	65	47.45%
	80-<90	43	31.39%
	≥90	3	2.19%
Marital status	Single	6	4.38%
	Married	115	83.94%
	Divorced	2	1.46%
	Separated	1	0.73%
	Widowed	10	7.30%
	Living with partner	2	1.46%
Level of education	Elementary school	0	0.00%
	Junior high school	23	16.79%
	High school	50	36.50%
	2-year college	4	2.92%
	4-year college	54	39.42%
	Graduate school	4	2.92%
	Decline to answer	1	0.73%
Employment status	Employed full-time	18	13.14%
	Self-employed	17	12.41%
	Part-time employed	6	4.38%
	Retired	62	45.26%
	Long-term disability	0	0.00%
	Short-term disability	0	0.00%
	Not employed (other than retired)	33	24.09%
Region of residence	Chubu	1	0.73%
	Kanto	105	76.64%
	Kyushu (including Okinawa)	30	21.90%
Household income	Less than ¥2,500,000	28	20.44%
	2,500,000 to ¥4,999,999	57	41.61%
	¥5,000,000 to ¥7,499,999	14	10.22%
	¥7,500,000 to ¥9,999,999	6	4.38%
	¥10,000,000 to ¥12,499,999	3	2.19%
	¥12,500,000 to ¥14,999,999	3	2.19%
	¥15,000,000 or more	2	1.46%
	Decline to answer	23	16.79%
Type of medical insurance	National health insurance	40	29.20%
	Late stage elderly insurance	76	55.47%
	Company/Social insurance	18	13.14%
	Welfare recipient	2	1.46%
	None of the above (all costs paid by myself/my family)	0	0.00%
Currently cared by a primary caregiver for prostate cancer	Yes	7	5.11%
	No	129	94.16%
Primary caregiver relationship	Wife	4	57.14%
	Child	1	14.29%

	Grandchild	0	0.00%
	Sibling	0	0.00%
	Other relative (parent, niece/nephew)	0	0.00%
	Hired professional caregiver	2	28.57%
	Other non-relative	0	0.00%
Physician-diagnosed comorbid condition	Cardiovascular disease	19	13.87%
	Chronic pulmonary disease	3	2.19%
	Rheumatologic disease	1	0.73%
	Peptic ulcer disease	16	11.68%
	Mild liver disease	13	9.49%
	Diabetes without chronic complications	16	11.68%
	Diabetes with chronic complications	5	3.65%
	Hemiplegia or paraplegia	1	0.73%
	Renal disease	4	2.92%
	Any malignancy, including leukemia and lymphoma	1	0.73%
	Moderate or severe liver disease	1	0.73%
	Other metastatic solid tumor currently being treated (other than that of the prostate)	1	0.73%
	AIDS/HIV	0	0.00%
	Hypertension	58	42.34%
	Prior malignancy, now in remission (malignancy other than that of the prostate)	10	7.30%
	None of the above	51	37.23%
		Mean	**SD**
Age		75.8	7.5

Supplementary table 2 List of attributes and levels in DCE

Attributes	Levels
i. Risk of fatigue as a side-effect of treatment	• 15% • 25% • 35%
ii. Risk of falls or fractures as a side-effect of treatment	• 3% • 10% • 20%
iii. Risk of cognitive impairment as a side-effect of treatment	• 0% • 5% • 10%
iv. Risk of hypertension as a side-effect of treatment	• 5% • 15% • 25%
v. Extension of time until cancer-related pain occurs	• 15 months • 35 months • 45 months
vi. Risk of rashes as a side-effect of treatment	• 5% • 15% • 25%

Supplementary table 3 Attribute-level preference weights: overall sample (N=137)

Attribute	Levels	Mean preference weight	SE	95% CI	p-value
Risk of fatigue as a side-effect of treatment	15%	0.633	0.035	0.564, 0.703	<0.001
	25%	0.034	0.013	0.009, 0.059	0.009
	35%	-0.667	0.043	-0.752, -0.582	<0.001
Risk of falls or fracture as a side- effect of treatment	3%	0.802	0.057	0.691, 0.913	<0.001
	10%	0.136	0.013	0.110, 0.161	<0.001
	20%	-0.938	0.054	-1.044, -0.831	<0.001
Risk of cognitive impairment as a side-effect of treatment	0%	1.385	0.058	1.271, 1.498	<0.001
	5%	0.035	0.012	0.012, 0.059	0.005
	10%	-1.420	0.056	-1.530, -1.310	<0.001
Risk of hypertension as a side-effect of treatment	5%	0.642	0.024	0.595, 0.689	<0.001
	15%	0.210	0.018	0.173, 0.246	<0.001
	25%	-0.852	0.037	-0.925, -0.779	<0.001
Extension of time until cancer-related pain occurs	15 months	-0.933	0.068	-1.066, -0.799	<0.001
	35 months	0.281	0.015	0.252, 0.309	<0.001
	45 months	0.652	0.064	0.526, 0.778	<0.001
Risk of rashes as a side-effect of treatment	5%	0.705	0.050	0.606, 0.803	<0.001
	15%	-0.056	0.016	-0.088, -0.024	<0.001
	25%	-0.648	0.051	-0.749, -0.548	<0.001

Supplementary table 4 Differences in preference weights across demographic and health history factors

			Risk of fatigue as a side-effect of treatment			Risk of falls or fracture as a side-effect of treatment			Risk of cognitive impairment as a side-effect of treatment			Risk of hypertension as a side-effect of treatment			Extension of time until cancer-related pain occurs			Risk of rashes as a side-effect of treatment		
		N	15%	25%	35%	3%	10%	20%	0%	5%	10%	5%	15%	25%	15 months	35 months	45 months	5%	15%	25%
Age group	<60	5	0.468	0.045	-0.513	0.429	0.123	-0.552	1.453	-0.083	-1.370	0.545	0.124	-0.794	-1.220	0.251	0.969	0.409	-0.093	-0.316
	60-<70	20	0.617	0.024	-0.641	0.755	0.170	-0.925	1.465	0.007	-1.472	0.646	0.174	-0.820	-1.015	0.274	0.741	0.728	-0.078	-0.651
	70-<80	65	0.620	0.021	-0.641	0.789	0.138	-0.927	1.362	0.055	-1.417	0.657	0.183	-0.840	-0.999	0.283	0.716	0.736	-0.037	-0.700
	≥80	46	0.691	0.059	-0.750	0.897	0.116	-1.013	1.353	0.031	-1.384	0.635	0.273	-0.908	-0.775	0.283	0.492	0.690	-0.074	-0.616
	p-value		0.621	0.602	0.595	0.455	0.621	0.479	0.922	0.119	0.966	0.849	0.096	0.745	0.380	0.978	0.297	0.683	0.689	0.548
Marital status	Married / Living with partner	117	0.646	0.034	-0.680	0.827	0.135	-0.961	1.373	0.043	-1.415	0.644	0.203	-0.847	-0.948	0.284	0.664	0.732	-0.060	-0.672
	Not	20	0.586	0.043	-0.629	0.686	0.135	-0.822	1.407	-0.012	-1.395	0.642	0.249	-0.891	-0.846	0.260	0.586	0.558	-0.040	-0.518
	p-value		0.558	0.797	0.687	0.394	0.980	0.377	0.837	0.113	0.902	0.975	0.396	0.744	0.608	0.568	0.679	0.234	0.681	0.303
Level of education	Completed university education	62	0.628	0.029	-0.657	0.785	0.141	-0.925	1.423	0.035	-1.457	0.625	0.219	-0.844	-0.899	0.290	0.609	0.699	-0.053	-0.646
	Not	75	0.647	0.040	-0.686	0.826	0.130	-0.956	1.339	0.035	-1.375	0.659	0.202	-0.862	-0.963	0.273	0.690	0.715	-0.061	-0.654
	p-value		0.790	0.677	0.733	0.721	0.681	0.784	0.476	0.970	0.467	0.487	0.656	0.802	0.640	0.566	0.532	0.879	0.821	0.939
Employment status	Employed	41	0.706	0.047	-0.753	0.879	0.149	-1.028	1.358	0.024	-1.382	0.667	0.228	-0.895	-0.994	0.279	0.714	0.740	-0.058	-0.682
	Not employed	96	0.609	0.030	-0.638	0.776	0.128	-0.905	1.386	0.040	-1.426	0.634	0.202	-0.836	-0.908	0.281	0.627	0.694	-0.057	-0.636
	p-value		0.211	0.533	0.228	0.409	0.476	0.301	0.824	0.555	0.723	0.532	0.531	0.456	0.569	0.945	0.536	0.675	0.989	0.685
Household income	Less than ¥5,000,000	85	0.644	0.037	-0.681	0.817	0.148	-0.965	1.413	0.038	-1.451	0.642	0.220	-0.862	-0.849	0.284	0.566	0.699	-0.051	-0.647
	¥5,000,000 to ¥9,999,999	20	0.660	0.062	-0.722	0.786	0.080	-0.866	1.263	0.019	-1.282	0.699	0.267	-0.966	-0.917	0.248	0.669	0.682	-0.040	-0.642
	¥10,000,000 or more	8	0.797	0.019	-0.816	1.191	0.090	-1.281	0.975	0.115	-1.090	0.669	0.150	-0.819	-1.453	0.398	1.055	0.864	-0.148	-0.717
	Decline to answer	24	0.540	0.010	-0.550	0.656	0.150	-0.807	1.486	0.010	-1.497	0.595	0.144	-0.738	-1.080	0.258	0.823	0.707	-0.063	-0.644
	p-value		0.468	0.701	0.533	0.274	0.253	0.297	0.237	0.297	0.335	0.677	0.227	0.353	0.164	0.177	0.206	0.893	0.571	0.991
Type of medical insurance	National health insurance	40	0.605	0.022	-0.627	0.746	0.137	-0.883	1.408	0.044	-1.452	0.628	0.196	-0.824	-0.989	0.272	0.718	0.685	-0.026	-0.659
	Late stage elderly insurance	76	0.677	0.040	-0.717	0.875	0.129	-1.004	1.348	0.047	-1.396	0.648	0.226	-0.874	-0.879	0.294	0.586	0.731	-0.070	-0.662
	Company/Social insurance	18	0.505	0.009	-0.513	0.587	0.163	-0.749	1.484	-0.029	-1.455	0.634	0.158	-0.793	-1.095	0.252	0.843	0.592	-0.067	-0.525
	Welfare recipient	2	1.017	0.342	-1.359	1.428	0.058	-1.486	0.904	-0.023	-0.880	0.894	0.343	-1.236	-0.445	0.225	0.221	1.292	-0.125	-1.167
	p-value		0.214	0.022	0.094	0.181	0.749	0.245	0.651	0.175	0.666	0.635	0.505	0.561	0.573	0.737	0.444	0.418	0.645	0.518
Currently cared by a primary caregiver for prostate cancer	Yes	7	0.665	0.058	-0.723	0.815	0.046	-0.861	1.137	0.071	-1.208	0.582	0.301	-0.883	-1.021	0.307	0.714	0.575	-0.062	-0.513
	No	129	0.636	0.034	-0.670	0.807	0.139	-0.946	1.390	0.033	-1.424	0.647	0.205	-0.852	-0.929	0.279	0.650	0.715	-0.057	-0.658
	p-value		0.858	0.678	0.789	0.975	0.116	0.731	0.334	0.480	0.398	0.551	0.254	0.805	0.769	0.681	0.827	0.542	0.944	0.536

Duration of prostate cancer (median split)	≤5 years	76	0.619	0.024	-0.643	0.808	0.135	-0.943	1.365	0.035	-1.401	0.635	0.197	-0.832	-0.994	0.295	0.699	0.700	-0.067	-0.633
	>5 years	60	0.662	0.049	-0.711	0.806	0.135	-0.941	1.393	0.035	-1.427	0.655	0.226	-0.882	-0.858	0.262	0.596	0.717	-0.045	-0.672
	p-value		0.553	0.337	0.443	0.984	0.990	0.986	0.815	0.969	0.815	0.676	0.427	0.538	0.327	0.270	0.431	0.867	0.511	0.709
ECOG grade at study enrolment	Grade 0	105	0.631	0.027	-0.658	0.811	0.135	-0.946	1.373	0.036	-1.409	0.639	0.205	-0.864	-0.973	0.282	0.690	0.719	-0.058	-0.661
	Grade 1	31	0.662	0.062	-0.724	0.796	0.132	-0.928	1.392	0.031	-1.423	0.661	0.227	-0.888	-0.802	0.275	0.527	0.669	-0.056	-0.613
	p-value		0.718	0.252	0.528	0.915	0.922	0.893	0.888	0.847	0.917	0.701	0.609	0.699	0.299	0.830	0.293	0.680	0.970	0.695
Symptomatic status at study enrolment	Symptomatic	3	0.853	-0.081	-0.772	0.979	0.097	-1.076	0.755	0.081	-0.836	0.547	0.124	-0.671	-1.990	0.252	1.739	1.039	-0.210	-0.829
	Asymptomatic	133	0.633	0.038	-0.671	0.803	0.136	-0.939	1.391	0.034	-1.425	0.646	0.212	-0.868	-0.910	0.281	0.629	0.700	-0.054	-0.646
	p-value		0.364	0.171	0.734	0.651	0.667	0.713	0.107	0.563	0.123	0.548	0.489	0.606	0.020	0.768	0.011	0.324	0.165	0.603

Supplementary table 5 Regression coefficients for preference weights and HRQoL sub-scale scores

		Risk of fatigue as a side-effect of treatment			Risk of falls or fracture as a side-effect of treatment			Risk of cognitive impairment as a side-effect of treatment			Risk of hypertension as a side-effect of treatment			Extension of time until cancer-related pain occurs			Risk of rashes as a side-effect of treatment		
	N	15%	25%	35%	3%	10%	20%	0%	5%	10%	5%	15%	25%	15 months	35 months	45 months	5%	15%	25%
Symptom scale: Urinary symptoms	137	0.002	0.000	-0.001	-0.001	0.001	0.000	0.003	0.000	-0.003	-0.001	0.002	0.001	0.004	-0.001	-0.004	-0.001	0.000	0.001
p-value		0.455	0.896	0.567	0.848	0.500	0.970	0.375	0.865	0.380	0.367	0.065	0.745	0.291	0.530	0.329	0.722	0.938	0.709
Symptom item: Incontinence aid	36	-0.004	-0.001	0.006	-0.007	-0.002	0.009	-0.001	-0.001	0.002	-0.004	-0.003	0.004	-0.005	0.000	0.005	-0.009	-0.001	0.010
p-value		0.022	0.052	0.012	0.020	0.103	0.003	0.741	0.148	0.519	0.011	0.545	0.060	0.249	0.596	0.247	0.002	0.524	0.002
Symptom scale: Bowel symptoms	137	-0.004	-0.001	0.004	-0.007	-0.001	0.009	0.004	-0.001	-0.003	-0.005	0.002	0.003	0.006	0.001	-0.007	-0.011	-0.001	0.012
p-value		0.256	0.603	0.280	0.144	0.217	0.068	0.428	0.564	0.487	0.020	0.233	0.368	0.303	0.366	0.195	0.013	0.370	0.006
Symptom scale: Hormonal treatment-related symptoms	137	0.004	0.000	-0.004	0.004	0.000	-0.003	-0.001	0.001	0.000	-0.002	0.000	0.002	0.001	0.003	-0.004	-0.002	0.000	0.002
p-value		0.148	0.908	0.224	0.422	0.725	0.451	0.894	0.472	0.988	0.315	0.834	0.486	0.800	0.036	0.460	0.608	0.908	0.590
Functional scales: Sexual activity	137	-0.002	0.000	0.003	-0.004	0.000	0.005	0.001	-0.003	0.002	-0.004	-0.003	0.007	-0.002	-0.001	0.003	-0.002	-0.002	0.004
p-value		0.587	0.852	0.619	0.546	0.843	0.498	0.850	0.054	0.835	0.227	0.131	0.127	0.830	0.734	0.761	0.716	0.367	0.519
Functional scales: Sexual functioning	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	17-18
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	12-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.