ANTICANCER RESEARCH *40*: 6443-6456 (2020)
doi:10.21873/anticanres.14666

Longitudinal Changes in Health-related Quality of Life After ^{125}I Low-dose-rate Brachytherapy for Localized Prostate Cancer

NAOYUKI OGASAWARA[1,2], MAKOTO NAKIRI[1], HIROFUMI KUROSE[1], KOSUKE UEDA[1], KATSUAKI CHIKUI[1], KIYOAKI NISHIHARA[1], MITSUNORI MATSUO[1], SHIGETAKA SUEKANE[1], KENTA MUROTANI[3], KOICHIRO MURAKI[4], CHIKAYUKI HATTORI[4], ETSUYO OGO[4], TUKASA IGAWA[1] and TATSUYA ISHITAKE[2]

[1]*Department of Urology, Kurume University School of Medicine, Kurume, Japan;*
[2]*Department of Environmental Medicine, Kurume University School of Medicine, Kurume, Japan;*
[3]*Biostatistics Center, Kurume University School of Medicine, Kurume, Japan;*
[4]*Department of Radiology, Kurume University School of Medicine, Kurume, Japan*

Abstract. *Background/Aim: The factors associated with longitudinal changes in health-related quality of life (HRQOL) are unclear. In this study we aimed to evaluate the longitudinal changes and predictors of HRQOL after ^{125}I low-dose-rate brachytherapy (LDB) for localised prostate cancer (PCA). Patients and Methods: We evaluated 180 patients with localised PCA treated with LDB. The HRQOL was evaluated at 3 weeks before LDB and at 1, 3, 6, 12, 18, 24, 36, and 48 months after LDB using the International Prostate Symptom Score, Medical Outcome Study 8-Items Short Form Health Survey (SF-8), and University of California Los Angeles Prostate Cancer Index (UCLA-PCI). Results: All HRQOL scores, except for UCLA-PCI sexual function and SF-8 mental component summary (MCS), were improved to baseline after an early transient deterioration. In contrast, the sexual function did not return to baseline after early deterioration. Meanwhile, the MCS scores showed no significant decline after implantation and trended upward. The prostate V100 and baseline UCLA-PCI sexual function scores predicted a clinically significant decrease in sexual function in the late post-implantation period. Conclusion: Most aspects of the HRQOL of PCA patients who underwent LDB improved to baseline. The results that V100 and baseline sexual function were predictors of late post-LDB may provide more accurate information for patients with preserved sexual function before treatment and for their partners.*

Correspondence to: Naoyuki Ogasawara, MD, Department of Urology, Kurume University School of Medicine 67 Asahi-machi, Kurume 830-0011, Japan. Tel: +81 942317572, Fax: +81 942317866, e-mail: nogasawara0030@yahoo.co.jp

Key Words: Prostate cancer, brachytherapy, health-related quality of life.

^{125}I low-dose-rate brachytherapy (LDB) is an effective treatment modality for clinically localised prostate cancer (PCA). LDB has been shown to achieve favorable oncological outcomes with a relatively low incidence of severe adverse events (1-5). Initially, LDB was indicated only in low-risk patients. However, it has been recently established as an effective treatment modality in combination with external beam radiotherapy (EBRT) and/or hormone therapy for intermediate and high-risk groups (6-7). Therefore, the use of LDB is projected to expand.

Treatment-related changes in quality of life, oncological outcomes, and adverse events are important factors in the decision-making for treatment. However, although there have been reports on the longitudinal changes in health-related quality of life (HRQOL) after LDB (8-11), few studies have reported on the factors associated with longitudinal changes in HRQOL (12-14). The examination of these factors will lead to a better understanding of the post-LDB course. Thus, the purpose of this study was to assess longitudinal changes in general and disease-specific HRQOL in patients with localised PCA who were treated with LDB. In addition, we examined the predictors associated with clinically significant longitudinal changes in HRQOL.

Patients and Methods

Study design and patients. This retrospective study was approved by the Institutional Review Board of the Kurume University Hospital and was conducted according to the tenets of the 1964

Declaration of Helsinki and its later amendments. Informed consent was obtained from all patients in this study.

We evaluated 334 patients who were treated with LDB for clinically localised PCA between March 2007 and December 2017 at Kurume University Hospital, Fukuoka, Japan. A total of 180 patients who could be followed for a minimum of 24 months and who could be assessed using the questionnaires were included in the analysis.

Treatment. The indication for LDB was based on the American Brachytherapy Society Consensus Guidelines (15). The patients were classified into risk groups according to the National Comprehensive Cancer Network (NCCN) risk classification (16). The low-risk and the intermediate-risk group with a Gleason score of 3+4 and a biopsy positive core rate of <33% received LDB monotherapy. Meanwhile, the remaining patients in the intermediate-risk group received additional EBRT. The high-risk group underwent LDB, EBRT, and hormone therapy for a duration of 9 months from pre-treatment to post-treatment.

Pathological diagnosis was established by a qualified pathologist in our Institution. A treatment plan based on transrectal ultrasonography was implemented 3 weeks before LDB. Neoadjuvant hormone therapy was administered for 3 months in patients with a prostate volume of ≥40 ml, trimodality, or at the surgeon's decision.

The prescribed dose was 145 Gy for LDB monotherapy and 110 Gy for combination therapy followed by an additional EBRT of 45 Gy. All implantations were performed using I-125 loose seeds and a Mick applicator (Mick Radio-Nuclear Instruments Inc., USA).

All implantations were based on interactive planning and modified peripheral loading methods. The initial 49 patients were implanted with an interplant software (CMS, St. Louis, MI, USA), while the latter 131 patients were implanted with a VariSeed software (Varian Medical Systems, Palo Alto, CA, USA). Dose-volume histograms for the prostate and urethra were constructed to determine the minimal dose of 90% of the prostate volume (D90), the volume of the prostate receiving 100% of the prescribed dose (V100), and the minimal dose received by 5% (UD5) and 30% (UD30) of the urethra. The post-implant dosimetric analysis was performed using computed tomography and magnetic resonance imaging conducted 4-5 weeks after LDB. The patients were generally discharged 2 days after implantation. Most patients were prescribed alpha-blockers (*e.g.* tamsulosin, silodosin, or naftopidil) or a phosphodiesterase 5 inhibitor (tadalafil), whereas some patients did not have any medication.

EBRT was carried out using intensity-modulated radiation therapy (IMRT) at 6-8 weeks after implantation with a total dose of 45 Gy/25 fractions. The radiation field of IMRT covered the prostate and seminal vesicles.

Follow-up and outcome measurements. Baseline patient characteristics, treatment parameters, and dosimetry factors were obtained from the medical records. The HRQOL was assessed using standard questionnaires at 3 weeks before LDB and at 1, 3, 6, 12, 18, 24, 36, and 48 months after LDB. The following were used as standard questionnaires:

IPSS. The International Prostate Symptom Score (IPSS) was used to assess lower urinary tract symptoms (LUTS) (17-18). The IPSS consists of eight questions, of which seven are related to symptoms and the remaining one is related to HRQOL. Each of the seven symptom-related questions is answered on a scale of 0 to 5. The one question related to HRQOL is answered on a scale of 0 to 6. The total IPSS is the sum of the individual scores of the seven symptom-related questions. The total IPSS is divided into the IPSS voiding score (sum of questions 1, 3, 5, and 6) and the IPSS storage score (sum of questions 2, 4, and 7). A higher score indicates poor conditions.

SF-8. The general HRQOL was assessed using the Medical Outcome Study 8-Items Short Form Health Survey (SF-8) (19-20). SF-8 consists of eight items that are aggregated into two summary scores: a physical component summary (PCS) and a mental component summary (MCS). HRQOL scores are shown as mean scores with standard deviation. PCS and MCS are calculated by weighting each SF-8 item using the norm-based scoring method. Each score is expressed based on a standard value of 50 points, which is the standard for the general Japanese population, thus it can be compared with the national average.

UCLA-PCI. The disease-specific HRQOL was assessed using the University of California Los Angeles Prostate Cancer Index (UCLA-PCI), which consists of 20 questions to assess urinary function, urinary bother, bowel function, bowel bother, sexual function, and sexual bother (21-22). The score ranges from 0 to 100 points, with higher scores indicating better conditions.

Statistical analysis. Baseline characteristics, treatment parameters, and dosimetry factors were compared between the two groups (monotherapy and EBRT combination therapy) using the Mann–Whitney test, Chi-squared test, and Fisher's exact test as appropriate. All questionnaire scores are shown as the mean score with the standard deviation. Mixed-effects linear regression models were used for longitudinal changes in all questionnaire scores, and Dunnett's multiple comparisons were used to compare measurement scores at each time point to the baseline score. For each questionnaire, a clinically meaningful change was defined as a change of at least one-half of the standard deviation at baseline (23). Univariate and multivariate logistic regression analyses were used to examine independent predictors associated with clinically significant changes in questionnaire scores at 24, 36, and 48 months. For multivariate analysis, age, neoadjuvant and adjuvant hormone therapy, EBRT, baseline HRQOL score, and factors with a p-value of ≤0.1 in the univariate analysis were selected as variables. All statistical analyses were performed using JMP version 14 (SAS Institute Inc., Cary, NC, USA). All tests were two-sided, and $p<0.05$ was considered statistically significant.

Results

The low-, intermediate-, and high-risk groups involved 56 (31.1%), 95 (52.8%), and 29 (16.1%) patients, respectively. Of the 180 patients, 107 patients were treated with LDB monotherapy, and 73 patients were treated with EBRT combination therapy. The median age of the overall cohort was 70 (51-83) years. The EBRT combination group was significantly older and had a higher age-adjusted Charlson Comorbidity Index (24) than did the LDB monotherapy group. Table I shows the baseline patient characteristics, treatment parameters, and dosimetry factors of the 180 patients.

Table I. *Patient characteristics at baseline. Data are presented as median (range) or number (percentage).*

Variable	Total (n=180)		LDR monotherapy (n=107)		ERBT combination (n=73)		*p*-Value
Age, years, median (range)	70	(51-83)	69	(54-83)	71	(51-81)	0.0247
BMI, kg/m^2, median (range)	23.4	(15.7-32.4)	23.1	(15.7-32.4)	23.8	(16.9-31.2)	0.4601
Initial PSA, ng/ml, median (range)	6.3	(2.34-135.1)	5.8	(2.34-17.5)	8.6	(2.85-135.1)	<0.0001
T stage, n (%)							
≤T2a	157	(87.2)	105	(98.1)	52.0	(71.2)	<0.0001
≥T2b	23	(12.8)	2	(1.9)	21.0	(28.8)	
Gleason score, n (%)							
≤ 3+4	126	(70.0)	106	(99.1)	20.0	(27.4)	<0.0001
≥4+3	54	(30.0)	1	(0.9)	53.0	(72.6)	
NCCN risk classification, n (%)							
Low	56	(31.1)	56	(52.3)	0	(0)	<0.0001
Intermediate	95	(52.8)	50	(46.7)	45	(61.6)	
High	29	(16.1)	1	(0.9)	28	(38.4)	
Positive core rate, %, median (range)	25.0	(4-100)	16.7	(6.3-66.7)	33.3	(4-100)	<0.0001
Prostate volume, ml, median (range)	25.5	(11.1-44.8)	28.0	(11.7-44.8)	22.2	(11.1-44.1)	<0.0001
Neoajuvant hormone therapy, n (%)							
Yes	97	(53.9)	61	(57.0)	51	(69.9)	0.0005
No	83	(46.1)	46	(43.0)	22	(30.1)	
Ajuvant hormone therapy, n (%)							
Yes	29	(16.1)	0	(0)	29	(39.7)	<0.0001
No	151	(83.9)	107	(0)	44	(60.3)	
Use of PDE5i, n (%)							
Yes	90	(50.0)	41.0	(38.3)	49.0	(67.1)	0.0002
No	90	(50.0)	66.0	(61.7)	24.0	(32.9)	
Number of seeds, median (range)	70	(34-105)	80	(50-105)	54	(34-76)	<0.0001
V100, %, median (range)	95.6	(75.3-100)	96.3	(88.2-100)	94.9	(75.34-99.9)	0.0049
V150, %, median (range)	71.6	(34.3-95.3)	74.3	(44.2-95.3)	66.7	(34.3-87.5)	<0.0001
D90, Gy, median (range)	156.5	(51.8-253.3)	172.7	(134.9-253.3)	124.7	(51.8-155.9)	<0.0001
UD5, Gy, median (range)	182.1	(92.9-395.3)	173.5	(92.9-395.3)	186.9	(135.8-293.1)	0.2936
UD30, Gy, median (range)	153.7	(88.7-274.3)	158.8	(88.7-274.3)	145.2	(106.7-197.3)	0.0001
RV100, ml, median (range)	0.1	(0-2.75)	0.2	(0-2.75)	0.1	(0-0.96)	0.2905
EBRT, n (%)							
Yes	73	(40.6)	0	(0)	73	(100)	<0.0001
No	107	(59.4)	107	(100.0)	0	(0)	
Occupation, n (%)							
Yes	91	(50.6)	61	(57.0)	30	(41.1)	0.0482
No	89	(49.4)	46	(43.0)	43	(58.9)	
Living with family, n (%)							
Yes	166	(92.2)	99	(92.5)	67	(91.8)	1.0000
No	14	(7.8)	8	(7.5)	6	(8.2)	
Alcohol drinking habit, n (%)							
Yes	129	(71.7)	77	77 (72.0)	52	(71.2)	1.0000
No	51	(28.3)	30	30 (28.0)	21	(28.8)	
Smoking habit, n (%)							
Yes	65	(36.1)	38	38 (35.5)	27	(37.0)	0.8752
No	115	(63.9)	69	69 (64.5)	46	(63.0)	
Sleep disorder, n (%)							
Yes	24	(13.3)	16	16 (15.0)	8	(11.0)	0.5080
No	156	(86.7)	91	91 (85.0)	65	(89.0)	
ACCI, n (%)							
≤3	56	(31.1)	44	(41.1)	12	(16.4)	0.0005
>3	124	(68.9)	63	(58.9)	61	(83.6)	
Follow up, median (range)	48	(24-84)	53	(24-84)	36	(24-73)	<0.0001

BMI: Body mass index; PSA: prostate-specific antigen; NCCN: National Comprehensive Cancer Network; PDE5i: phosphodiesterase-5-inhibitor; V100: the prostate volume receiving 100% of the prescribed minimal dose; V150: the prostate volume receiving 150% of the prescribed minimal dose; D90: the minimal dose received by 90% of the prostate; UD5: the minimal dose received by 5% of the urethra; UD30: the minimal dose received by 30% of the urethra; RV100: volume of rectum receiving 100% of the prescribed dose; EBRT: external beam radiotherapy; ACCI: age-adjusted Charlson comorbidity index.

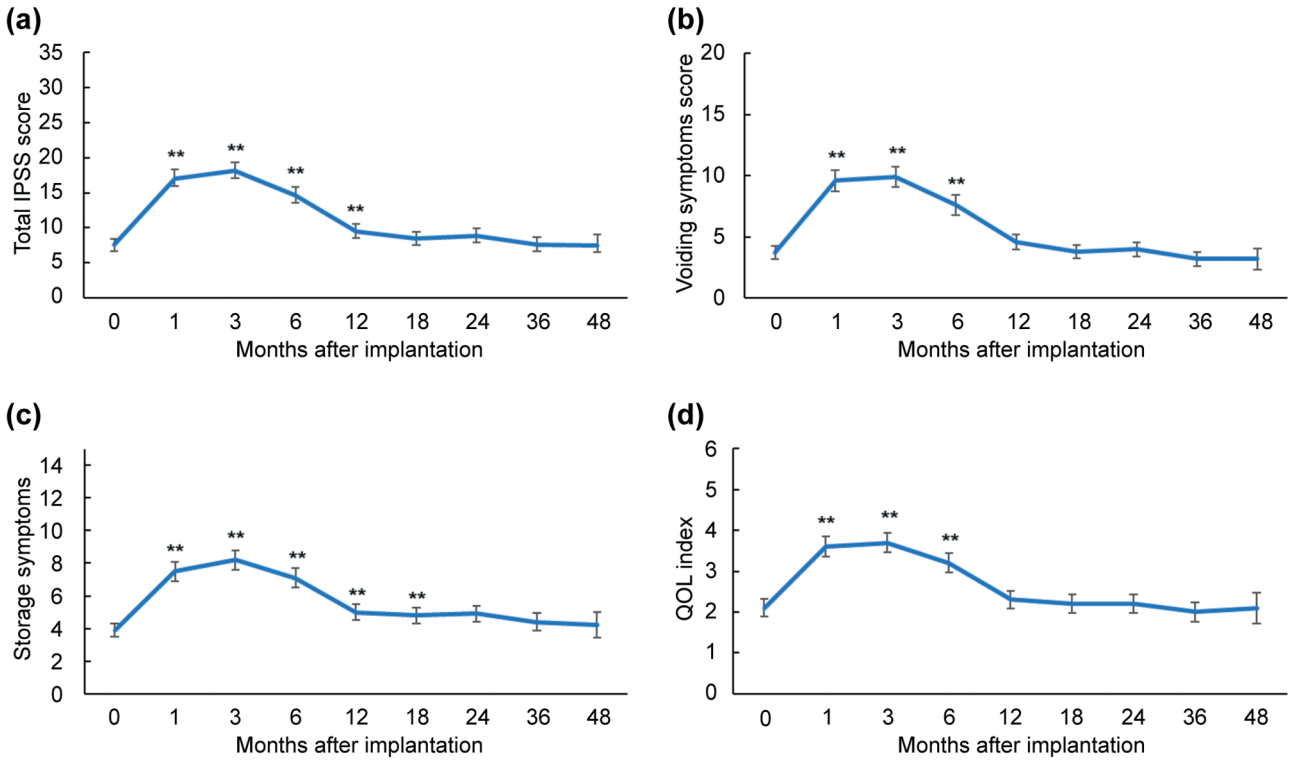

Figure 1. *Longitudinal changes of Total IPSS (a), voiding symptom (b), storage symptom scores (c), and IPSS-QOL index (d) after LDB in all patients. High scores indicate better outcomes. Error bars represent 95% confidence intervals. All score: Mean score, error bars: 95% confidence intervals, asterisks (*): p<0.05, double asterisks (**): p<0.01 (compared to baseline using Dunnett's multiple comparisons). IPSS: International Prostate Symptom Score; QOL: quality of life; LDB: ^{125}I low-dose-rate brachytherapy.*

For treatment parameters, neoadjuvant and adjuvant hormone therapy were administered to 97 (53.5%) and 29 (16.1%) patients, respectively. Neoadjuvant hormone therapy was significantly more common in the EBRT combination group, and all adjuvant hormone therapies were administered in the EBRT combination group.

For dosimetry factors, the median V100, 150% of the prescribed minimal dose (V150), and D90 were 95.6%, 71.6%, and 156.5 Gy, respectively. The median UD5 and UD30 were 182.1 Gy and 153.7 Gy, respectively. The median rectum volume receiving 100% of the prescribed minimal dose (RV100) was 0.1 ml. The monotherapy group had a significantly higher V100 (96.3% *vs.* 94.9%, p=0.0049), V150 (74.3% *vs.* 66.7%, p<0.0001), D90 (172.7 Gy *vs.* 124.7 Gy, p<0.0001), and UD30 (158.8 Gy *vs.* 145.2 Gy, p=0.0001) than the EBRT group. Meanwhile, there was no significant difference in UD5 and RV100 between the two treatment groups.

The percentage of people working and earning an income was significantly higher in the monotherapy group than that in the EBRT combination therapy group, but the other characteristics (*e.g.*, living with a family, alcohol drinking habits, smoking habits, and sleep disorders) were not significantly different between the two treatment groups. The median follow-up duration was 48 months. Only three patients (1.7%) had biochemical relapse during the observation period.

Longitudinal changes in IPSS after implantation. In the overall cohort, the total IPSS, voiding score, storage score, and IPSS-QOL index increased early after implantation and peaked at 3 months. The IPSS storage score returned to baseline more slowly than the other scores did at 24 months after implantation. Meanwhile, the total IPSS, voiding score, and IPSS-QOL index returned to baseline at 12-18 months (Figure 1a-d). There was no significant difference in all IPSS-related scores between the LDB monotherapy group and the EBRT combination therapy group from baseline to 48 months after implantation (Figure 2a-d).

Longitudinal changes in general HRQOL (SF-8) after implantation. In the overall cohort, the MCS scores showed no significant decline after implantation and were higher than the national average at all time points and trended

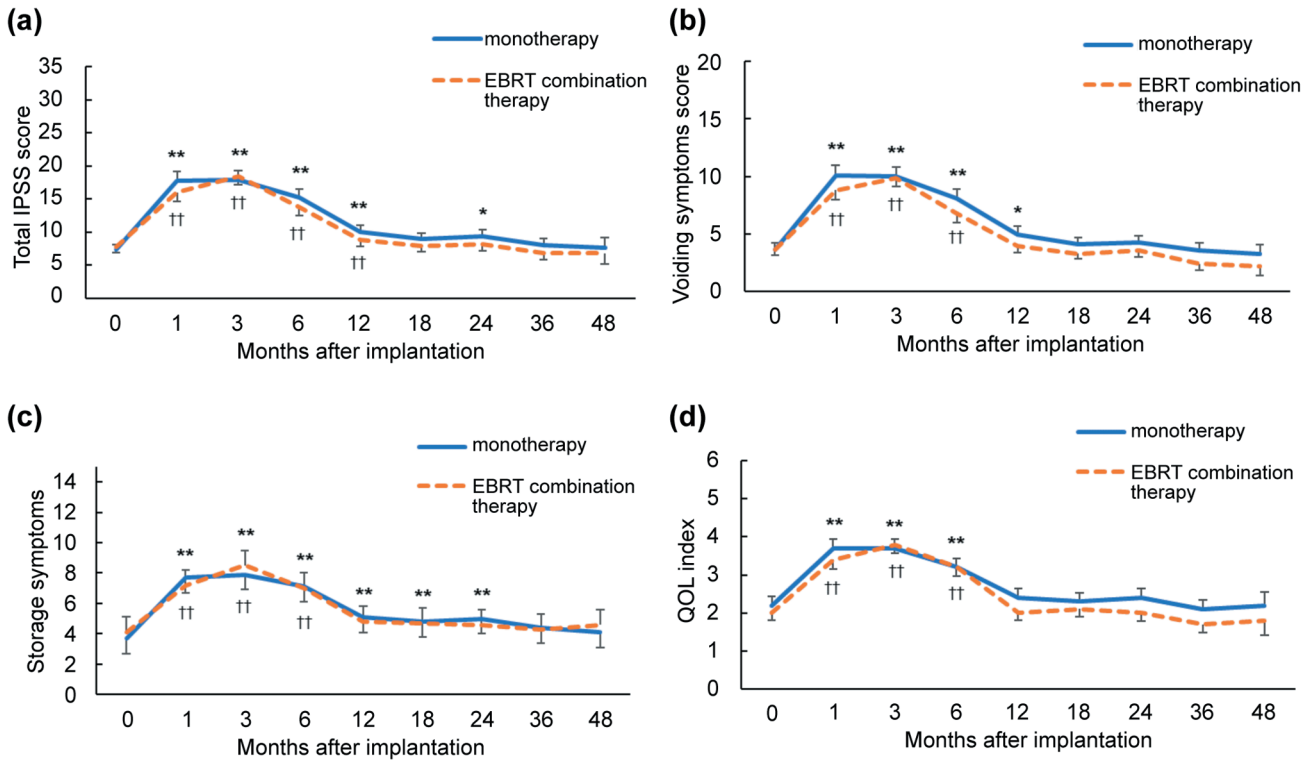

Figure 2. *Longitudinal changes of Total IPSS (a), voiding symptom (b), storage symptom scores (c), and IPSS-QOL index (d) after LDB in the monotherapy group and the EBRT combination therapy group. High scores indicate better outcomes. All score: Mean score, error bars: 95% confidence intervals; confidence intervals were symmetric, but error bars are shown as one-sided to avoid overlap with mean scores. Solid line: monotherapy group, dotted line: EBRT combination group, asterisks (*): p<0.05, double asterisks (**): p<0.01 (compared to baseline using Dunnett's multiple comparisons in monotherapy group), daggers (†): p<0.05, double daggers (††): p<0.01 (compared to baseline using Dunnett's multiple comparisons in EBRT combination group). IPSS: International Prostate Symptom Score; QOL: quality of life; LDB: ^{125}I low-dose-rate brachytherapy; EBRT: external beam radiotherapy.*

upward (Figure 3a). In contrast, the PCS scores decreased early after implantation, showed the lowest score at 3 months, and returned to baseline levels at 12 months. The PCS scores were equal to the national average, except for the early transient decrease after implantation (Figure 3b).

There was no significant difference in MCS scores between the LDB monotherapy group and the EBRT combination therapy group from baseline to 48 months after implantation (Figure 4a). In contrast, there was an interaction in PCS scores between the two groups. The PCS scores showed a similar trend until 36 months, with a significant difference at 48 months between the two treatment groups (Figure 4b).

Longitudinal changes in disease-specific HRQOL (UCLA-PCI) after implantation. The urinary function scores decreased early after implantation, showed the lowest score at 3 months, and finally returned to baseline at 48 months (Figure 5a). The urinary bother scores decreased early after implantation, showed the lowest score at 1 month, and returned to baseline at 12 months (Figure 5b). The bowel function and bother scores decreased early after implantation, showed the lowest score at 3 months, and returned to baseline at 6 months (Figure 5c-d). The sexual function scores decreased early after implantation, showed the lowest score at 3 months, and returned to baseline at 12 months, although they significantly decreased again after 36 months (Figure 5e). The sexual bother scores decreased early after implantation, showed the lowest score at 3 months, and returned to baseline at 6 months (Figure 5f).

There was no significant difference in urinary function, urinary bother, and bowel function between the LDB monotherapy and EBRT combination therapy groups throughout the 4-year evaluation period (Figure 6a-c). The bowel bother score showed an interaction between the two treatment groups (interaction $p<0.0001$). However, the bowel bother score was only significantly different between the two treatment groups at 3 months after implantation, with the EBRT combination therapy group showing a significantly

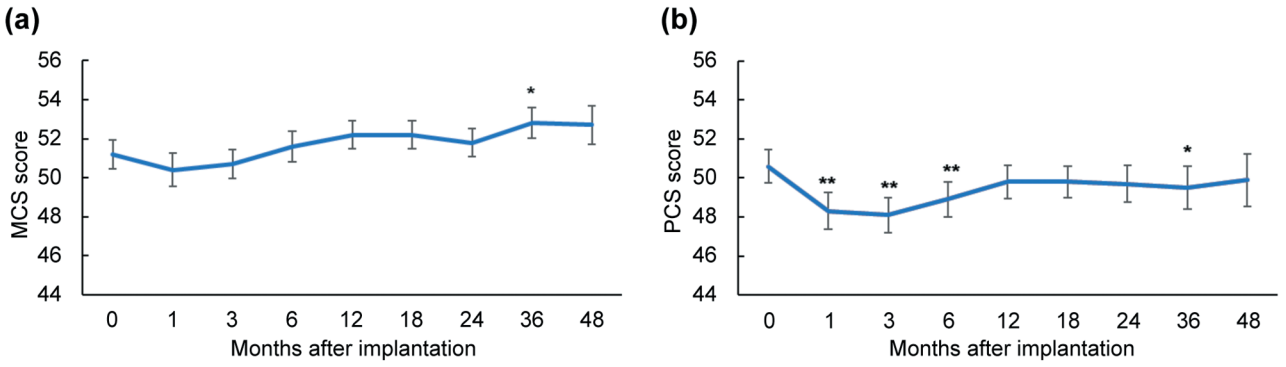

Figure 3. *Longitudinal changes of SF-8 MCS (a) and PCS (b) after LDB in all patients. High scores indicate better outcomes. All score: mean score, error bars: 95% confidence intervals, asterisks (*): p<0.05, double asterisks (**): p<0.01 (compared to baseline using Dunnett's multiple comparisons). SF-8: Medical Outcome Study 8-Items Short Form Health Survey; MCS: mental component summary; PCS: physical component summary; LDB: ^{125}I low-dose-rate brachytherapy.*

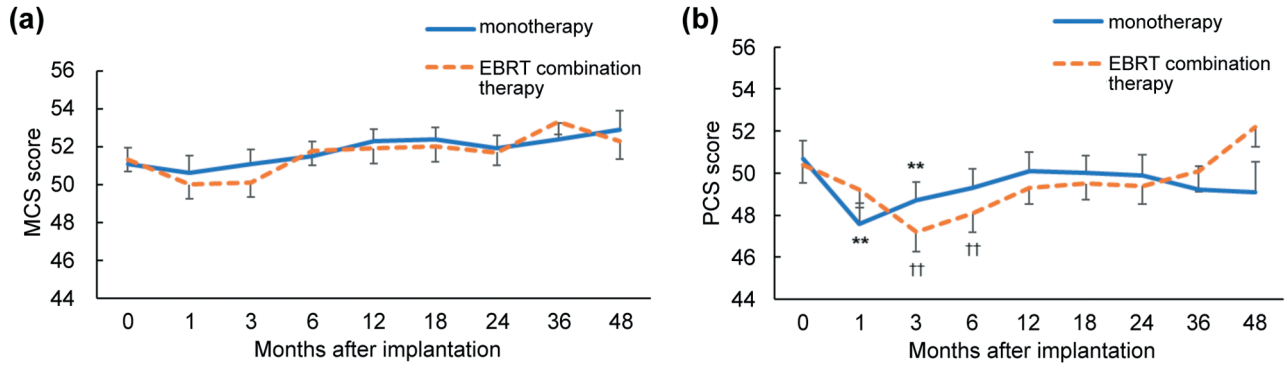

Figure 4. *Longitudinal changes of SF-8 MCS (a) and PCS (b) after LDB in the monotherapy group and the EBRT combination therapy group. High scores indicate better outcomes. All score: Mean score, error bars: 95% confidence intervals; confidence intervals were symmetric, but error bars are shown as one-sided to avoid overlap with mean scores. Solid line: monotherapy group, dotted line: EBRT combination group, asterisks (*): p<0.05, double asterisks (**): p<0.01 (compared to baseline using Dunnett's multiple comparisons in monotherapy group), daggers (†) : p<0.05, double daggers (††): p<0.01 (compared to baseline using Dunnett's multiple comparisons in EBRT combination group). SF-8: Medical Outcome Study 8-Items Short Form Health Survey; MCS: mental component summary; PCS: physical component summary; LDB: ^{125}I low-dose-rate brachytherapy; EBRT: external beam radiotherapy.*

lower score (Figure 6d). The sexual function scores showed an interaction between the two treatment groups (interaction p=0.0075). After an early post-implantation decrease, it quickly returned to baseline in the monotherapy group, whereas it did not in the EBRT combination therapy group. The sexual function of the LDB monotherapy group was higher than that of the EBRT combination group at all measurement timepoints except at 48 months (Figure 6e). Meanwhile, although the LDB monotherapy group showed higher sexual bother score than did the EBRT combination group throughout the 4-year evaluation, the difference was not significant (Figure 6f).

Multivariate analysis of clinically significant changes during the late observation period. In the overall cohort, the UCLA-PCI sexual function score did not return to baseline after the early deterioration. In contrast, the MCS score showed no significant decline after implantation and even trended upward. These trends were distinctive and different from the other questionnaire scores. Therefore, univariate and multivariate logistic regression analyses were performed to examine factors associated with clinically significant changes in sexual function and MCS during the late post-implantation period (*i.e.*, 24, 36, and 48 months).

Table II shows the univariate and multivariate logistic regression analyses for a decrease in sexual function. Only prostate V100 and sexual function scores at baseline were identified as common predictors of a clinically significant decrease in sexual function at 24, 36, and 48 months.

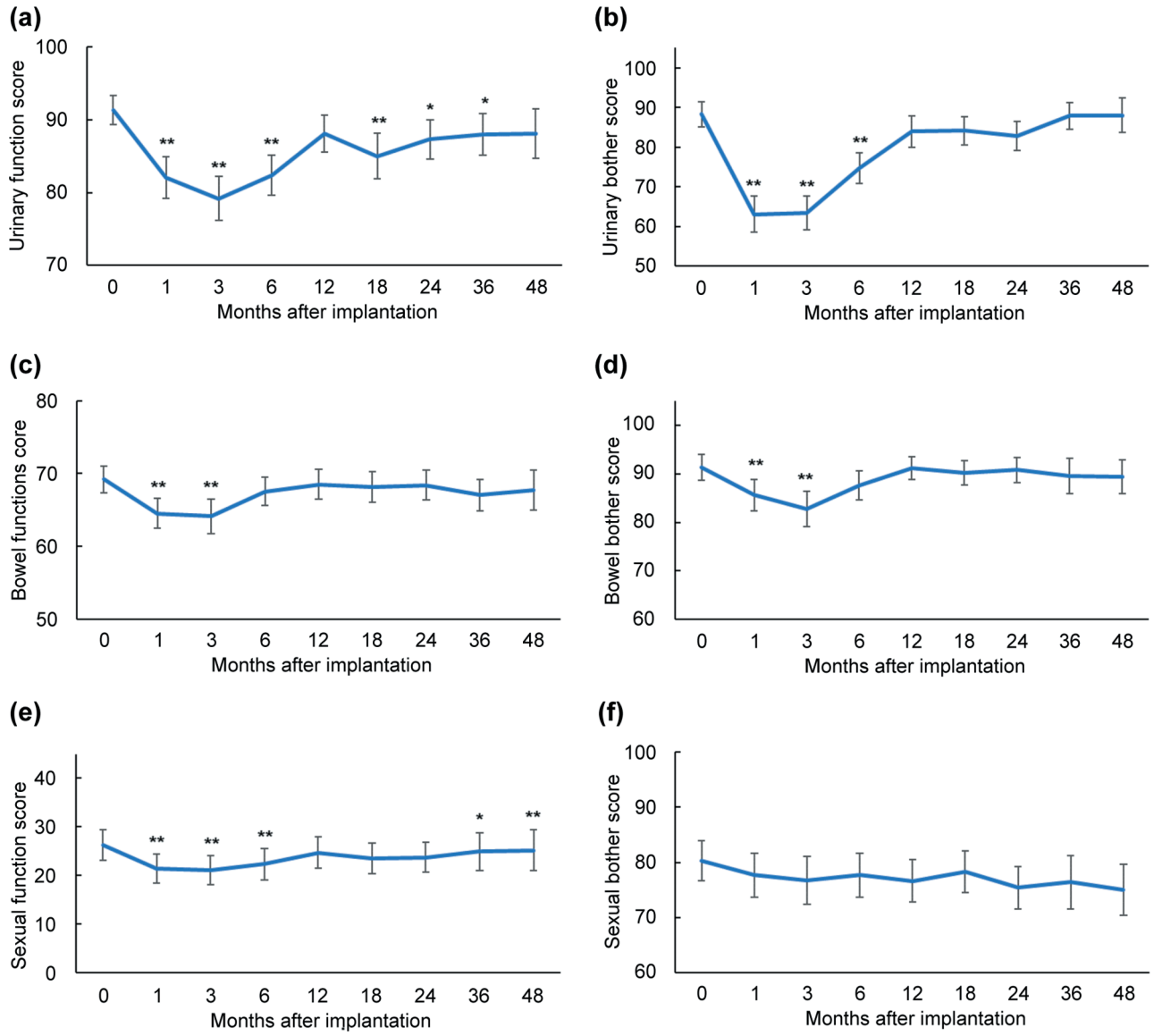

Figure 5. *Longitudinal changes of UCLA-PCI urinary function(a), urinary bother (b), bowel function (c), bowel bother (d), sexual function (e), and sexual bother scores (f) after LDB in all patients. High scores indicate better outcomes. All score: Mean score, error bars: 95% confidence intervals, asterisks (*): p<0.05, double asterisks (**): p<0.01 (compared to baseline using Dunnett's multiple comparisons). UCLA-PCI: University of California Los Angeles Prostate Cancer Index; LDB: ^{125}I low-dose-rate brachytherapy.*

Table III shows the univariate and multivariate logistic regression analyses for MCS increase. Only the MCS score at baseline was identified as a factor associated with a clinically significant increase in MCS at 24, 36, and 48 months.

Discussion

Treatment-related changes in HRQOL are important factors in the decision-making process for the treatment of patients with localized PCA. In addition, the knowledge of factors associated with longitudinal changes in HRQOL will lead to a better understanding of the post-LDB course. In this study, all HRQOL scores, except for UCLA-PCI sexual function and SF-8 MCS, returned to baseline after the early transient deterioration. In contrast, the UCLA-PCI sexual function did not after an early deterioration. Meanwhile, the MCS scores showed no significant decline after implantation, were higher than the national average at all time points, and even trended upward.

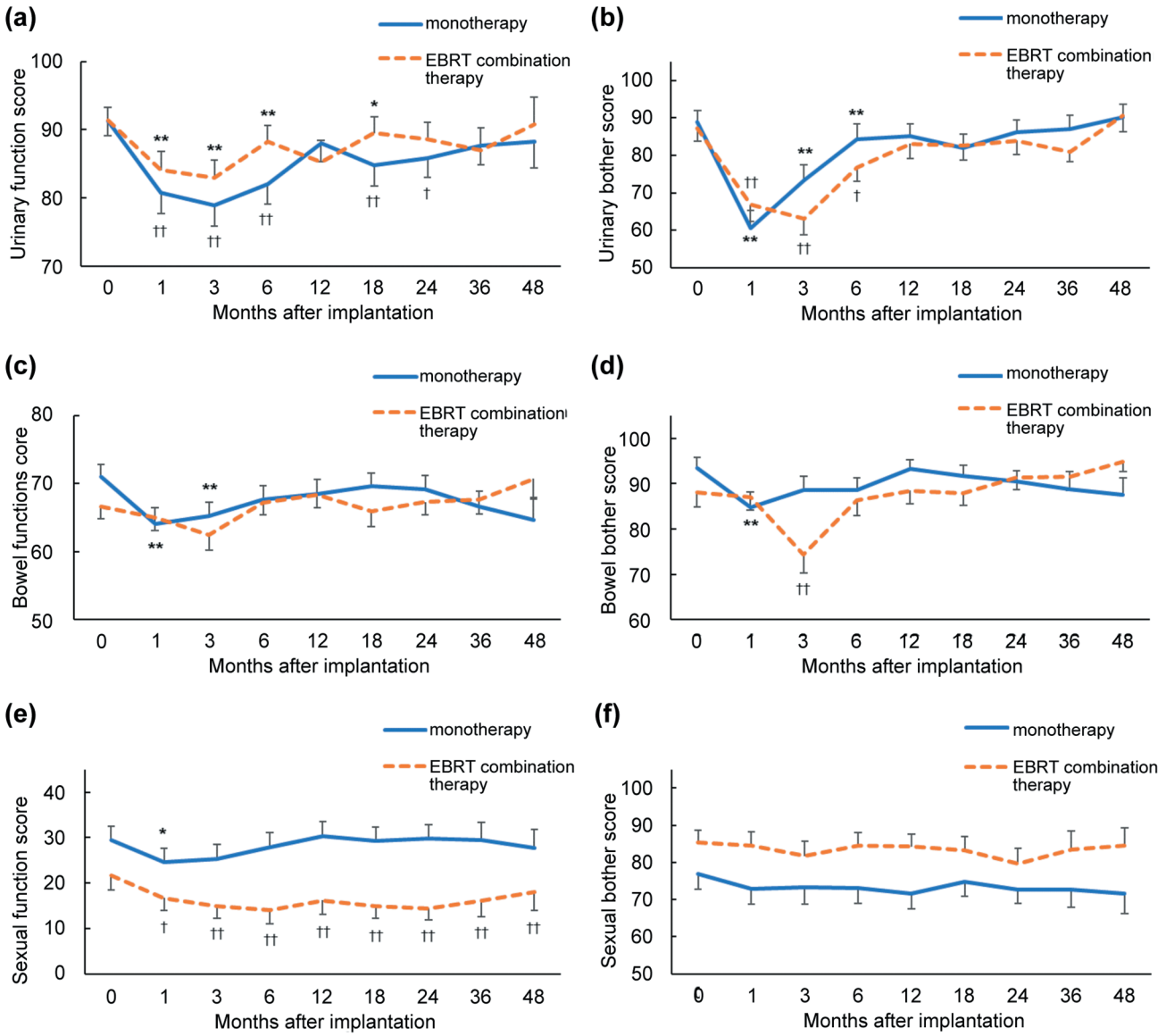

Figure 6. *Longitudinal changes of UCLA-PCI urinary function(a), urinary bother (b), bowel function(c), bowel bother (d), sexual function(e), and sexual bother scores (f) after LDB in the monotherapy group and the EBRT combination therapy group. High scores indicate better outcomes. All score: Mean score, error bars: 95% confidence intervals; confidence intervals were symmetric, but error bars are shown as one-sided to avoid overlap with mean scores. Solid line: monotherapy group, dotted line: EBRT combination group, asterisks (*): p<0.05, double asterisks (**): p<0.01 (compared to baseline using Dunnett's multiple comparisons in monotherapy group), daggers (†) : p<0.05, double daggers (††): p<0.01 (compared to baseline using Dunnett's multiple comparisons in EBRT combination group). UCLA-PCI: University of California Los Angeles Prostate Cancer Index; LDB: ^{125}I-Low-dose-rate brachytherapy; EBRT: external beam radiotherapy.*

When the patients were divided into the LDB monotherapy and the EBRT combination therapy groups, the EBRT combination group was significantly older and had more comorbidities than the LDB monotherapy group. However, there was no difference in the trends between the two groups, except for sexual function and sexual bother.

Iinuma *et al*. conducted a long-term analysis of LUTS after LDB (with and without EBRT) using IPSS. The total IPSS and IPSS-QOL index showed an immediate decrease after LDB, although it returned to baseline at 18 to 36 months. Compared with the LDB monotherapy group, the combination therapy group showed worse total IPSS scores than did the monotherapy group. Further, the total IPSS

Table II. *Univariate and multivariate analysis of predictors associated with clinically significant decreases of sexual function scores at ≥24months after implantation.*

Variable	24 months (n=174)								36 months (n=128)								48 months (n=92)							
	Univariate				Multivariate				Univariate				Multivariate				Univariate				Multivariate			
	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value
Age at implant																								
≥70	1.186	0.594	2.382	0.628	2.726	0.929	8.285	0.068	1.073	0.394	2.777	0.886	1.797	0.726	4.445	0.205	0.652	0.272	1.528	0.327	0.932	0.312	2.792	0.899
<70	1				1				1				1				1				1			
BMI	1.027	0.912	1.157	0.657					0.915	0.799	1.041	0.177					0.989	0.844	1.158	0.890				
Clinical T stage																								
≥T2b	0.682	0.500	0.188	1.976					0.484	0.104	1.684	0.267					1.021	0.191	4.904	0.979				
≤T2a	1								1								1							
Initial PSA	0.992	0.925	1.025	0.689					0.984	0.911	1.019	0.420					0.981	0.882	1.018	0.380				
Gleason score																								
≥4+3	1.213	0.566	2.524	0.612					0.997	0.417	2.304	0.995					0.827	0.232	2.705	0.756				
≤3+4	1								1								1							
Positive core rate	1.003	0.984	1.021	0.763					1.003	0.983	1.022	0.797					0.996	0.973	1.019	0.747				
Prostate volume	1.008	0.962	1.056	0.729					0.894	0.174	4.512	0.892					0.994	0.973	1.055	0.852				
NAHT																								
Yes	0.421	0.204	0.848	0.015	0.740	0.249	2.116	0.575	0.236	0.104	0.509	0.0002	0.415	0.143	1.207	0.106	0.214	0.079	0.532	0.0007	0.518	0.136	1.894	0.318
No	1				1				1				1				1				1			
AHT																								
Yes	1.069	0.393	2.638	0.889	1.263	0.297	5.272	0.748	0.660	0.173	2.110	0.496	1.280	0.229	7.143	0.779	0.519	0.072	2.557	0.432	2.765	0.225	30.989	0.410
No	1				1				1				1				1				1			
Number of seeds	0.990	0.968	1.012	0.370					0.987	0.963	1.011	0.302					0.997	0.959	2.782	0.348				
V100 (%)	1.129	1.007	1.285	0.037	1.180	1.022	1.384	0.023	1.175	1.042	1.350	0.0069	1.188	1.030	1.394	0.025	1.127	0.989	1.320	0.075	1.209	1.012	1.479	0.036
V150 (%)	1.002	0.975	1.031	0.871					1.010	0.981	1.040	0.515					0.967	1.043	1.004	0.834				
D90 (Gy)	1.008	0.985	1.033	0.495					1.003	0.991	1.015	0.659					1.018	0.988	1.052	0.246				
UD5 (Gy)	0.998	0.991	1.004	0.516					1.000	0.993	1.006	0.946					1.002	0.994	1.010	0.587				
UD30 (Gy)	0.998	0.984	1.012	0.829													0.995	0.976	1.013	0.561				
RV100 (ml)	1.323	0.621	2.687	0.452					1.839	0.872	4.101	0.110					1.045	0.470	2.274	0.911				
EBRT																								
Yes	2.100	1.046	4.257	0.037	5.706	2.043	17.171	0.0008	1.004	0.990	1.018	0.582	3.714	1.253	11.005	0.018	1.909	0.747	4.968	0.176	2.714	0.716	11.310	0.143
No	1				1				1				1				1				1			
ACCI																								
>3	1.101	0.529	2.383	0.799					1.201	0.570	2.581	0.632					0.707	0.304	1.638	0.418				
≤3	1								1								1							
Baseline IPSS																								
≥moderate	0.63	0.306	1.267	0.197					0.480	0.222	1.008	0.052	0.790	0.309	2.021	0.623	0.582	0.245	1.346	0.207				
mild	1								1				1				1							
Baseline sexual function	1.053	1.034	1.075	<0.0001	1.072	1.046	1.102	<0.0001	1.050	1.030	1.073	<0.0001	1.050	1.024	1.079	0.0002	1.064	1.039	1.095	<0.0001	1.069	1.036	1.109	<0.0001
Use of PDE5i																								
Yes	0.768	0.381	1.532	0.454					0.816	0.388	1.693	0.586					1.025	0.375	2.734	0.961				
No	1								1								1							
Smoking habit																								
Yes	1.407	0.688	2.846	0.346					1.390	0.650	2.955	0.393					1.609	0.676	3.858	0.282				
No	1								1								1							
Drinking habit (alcohol)																								
Yes	0.884	0.421	1.926	0.750					0.795	0.364	1.763	0.569					1.101	0.445	2.788	0.836				
No	1								1								1							

BMI: Body mass index; PSA: prostate-specific antigen; NAHT: neoadjuvant hormone therapy; AHT: adjuvant hormone therapy; V100: the prostate volume receiving 100% of the prescribed minimal dose; V150: the prostate volume receiving 150% of the prescribed minimal dose; D90: the minimal dose received by 90% of the prostate; UD5: the minimal dose received by 5% of the urethra; UD30: the minimal dose received by 30% of the urethra; RV100: volume of rectum receiving 100% of the prescribed dose; EBRT: external beam radiotherapy; ACCI: age-adjusted Charlson comorbidity index; IPSS: International Prostate Symptom Score; PDE5i: phosphodiesterase-5-inhibitor.

Table III. *Univariate and multivariate analysis of predictors associated with clinically significant increases of MCS scores at ≥24months after implantation.*

Variable	24 months (n=176)								36 months (n=128)								48 months (n=92)							
	Univariate				Multivariate				Univariate				Multivariate				Univariate				Multivariate			
	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value
Age at implant																								
≥70	1.533	0.818	2.902		1.871	0.573	6.110	0.300	1.471	0.717	3.035	0.293	1.624	0.653	4.141	0.298	1.440	0.611	3.402	0.403	1.466	0.478	4.604	0.502
<70	1				1				1				1				1				1			
BMI	1.005	0.901	1.121	0.927					0.910	0.025	1.729	0.152					0.972	0.826	1.140	0.727				
Clinical T stage																								
≥T2b	1.440	0.560	3.565	0.439					2.106	0.658	6.944	0.207					2.208	0.459	11.813	0.317				
≤T2a	1								1								1							
Initial PSA	1.009	0.977	1.048	0.546					1.020	0.987	1.084	0.250					1.018	0.984	1.099	0.318				
Gleason score																								
≥4+3	0.837	0.410	1.660	0.615					0.789	0.323	1.836	0.588					0.968	0.271	3.174	0.957				
≤3+4	1								1								1							
Positive core rate	0.989	0.971	1.006	0.214					0.991	0.971	1.011	0.402					0.987	0.962	1.010	0.286				
Prostate volume	0.985	0.943	1.028	0.493					0.987	0.937	1.038	0.614					0.985	0.927	1.046	0.629				
NAHT																								
Yes	0.773	0.412	1.449	0.422	1.051	0.401	2.755	0.920	0.543	0.258	1.119	0.098	0.809	0.294	2.190	0.677	0.508	0.205	1.209	0.127	0.546	0.150	1.825	0.329
No	1				1				1				1				1				1			
AHT																								
Yes	0.761	0.297	1.792	0.541	0.955	0.224	4.067	0.951	0.636	0.166	2.032	0.457	0.994	0.159	5.558	0.995	1.182	0.221	5.688	0.834	3.302	0.309	37.373	0.320
No	1				1				1				1				1				1			
Number of seeds	0.998	0.978	1.018	0.825					1.001	0.977	1.025	0.928					0.999	0.971	1.029	0.971				
V100 (%)	0.981	0.897	1.076	0.680					0.981	0.890	1.084	0.706					0.986	0.875	1.114	0.810				
V150 (%)	0.997	0.973	1.023	0.840					1.01	0.982	1.04	0.496					1.027	0.988	1.070	0.180				
D90 (Gy)	1.003	0.993	1.014	0.525					1.005	0.993	1.017	0.456					1.001	0.986	1.016	0.906				
UD5 (Gy)	1.007	1.002	1.013	0.0089	1.006	0.999	1.014	0.094	1.003	0.997	1.010	0.289					1.005	0.997	1.013	0.226				
UD30 (Gy)	1.004	0.997	1.010	0.257					1.005	0.998	1.013	0.172					1.010	1.000	1.021	0.061	1.026	1.001	1.055	0.040
RV100 (ml)	0.566	0.241	1.182	0.135					1.185	0.566	2.481	0.654					0.973	0.425	2.120	0.946				
EBRT																								
Yes	0.855	0.445	1.619	0.632	0.685	0.234	2.008	0.491	0.799	0.367	1.698	0.563	0.805	0.258	2.379	0.697	1.154	0.439	2.965	0.768	0.924	0.220	3.594	0.910
No	1				1				1				1				1				1			
ACCI																								
>3	1.524	0.768	3.133	0.232	1.661	0.417	6.610	0.472	1.265	0.602	2.715	0.537					1.179	0.504	2.802	0.706				
≤3	1				1				1								1							
Baseline IPSS																								
≥moderate	1.536	0.820	2.896	0.180					1.205	0.584	2.484	0.612					1.284	0.551	2.998	0.562				
mild	1								1								1							
Baseline MCS	0.660	0.572	0.744	<0.0001	0.644	0.548	0.734	<0.0001	0.672	0.569	0.770	<0.0001	0.670	0.565	0.770	<0.0001	0.719	0.605	0.824	<0.0001	0.716	0.597	0.826	<0.0001
Occupation																								
Yes	0.918	0.490	1.719	0.790					0.860	0.419	1.764	0.681					0.779	0.334	1.816	0.562				
No	1								1								1							
Living with family																								
Yes	1.146	0.356	4.380	0.826					2.556	0.608	17.428	0.214					1.667	0.338	12.099	0.544				
No	1								1								1							

Table III. *Continued*

Table III. *Continued*

Variable	24 months (n=176)							36 months (n=128)							48 months (n=92)						
	Univariate				Multivariate			Univariate				Multivariate			Univariate				Multivariate		
	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value	OR	95%CI		*p*-Value
Smoking habit																							
Yes	0.648	0.324	1.258	0.202				0.724	0.329	1.550	0.409				1.101	0.453	2.640	0.830				
No	1							1							1							
Drinking habits (alcohol)																						
Yes	1.252	0.625	2.591	0.531				1.154	0.526	2.608	0.724				0.909	0.365	2.310	0.839				
No	1							1							1							
Sleepdisorder																						
Yes	2.460	1.009	6.062	0.048	0.523	0.140	1.959	0.336	1.800	0.618	5.250	0.276			1.690	0.529	5.412	0.370				
No	1				1				1						1							

BMI: Body mass index; PSA: prostate-specific antigen; NAHT: neoadjuvant hormone therapy; AHT: adjuvant hormone therapy; V100: the prostate volume receiving 100% of the prescribed minimal dose; V150: the prostate volume receiving 150% of the prescribed minimal dose; D90: the minimal dose received by 90% of the prostate; UD5: the minimal dose received by 5% of the urethra; UD30: the minimal dose received by 30% of the urethra; RV100: volume of rectum receiving 100% of the prescribed dose; EBRT: external beam radiotherapy; ACCI: age-adjusted Charlson comorbidity index; IPSS: International Prostate Symptom Score; MCS: Mental Component Summary in SF-8.

scores decreased after transient improvement in the late observation period in the combination therapy group (18). The transient recurrence of urinary symptoms after an asymptomatic period is referred to as a "urinary symptom flare" and is a late complication of LDB (25). In this study, the total IPSS showed a similar trend in all patients, but there was no significant difference between the monotherapy and EBRT combination groups. Multiple factors such as concomitant EBRT, age, IPSS, erectile dysfunction, and biologically effective dose have been associated with urinary symptom flare (26-28), and this may explain our results.

For the IPSS voiding score and storage score, the storage score returned more slowly than did the voiding score, consistent with previous reports (29-30). In this study, the SF-8 MCS showed an upward trend with no significant decrease in the early posttreatment period. In addition, the SF-8 MCS was higher than the national standard score at all measurement points. Koga *et al*. conducted a large prospective HRQOL study using the SF-8 and EPIC, and they showed a similar trend of MCS (11). This has been explained as a phenomenon called benefit finding or posttraumatic growth (31). In this study, we examined factors associated with the clinically significant increases in MCS in multivariate analysis, but only the baseline MCS score was identified. Many factors were related to MCS; thus, it may have been difficult to identify factors associated with clinically significant changes in MCS.

In this study, the SF-8 PCS decreased early after implantation, showed the lowest score at 3 months, and returned to baseline levels at 12 months. Koga *et al*. reported a significantly lower PCS at 36 months (11). Roeloffzen *et al*. also reported similar results in a 6-year prospective study (12). However, these reports showed only statistically significant decreases and not clinically significant decreases. Punenn *et al*. conducted a prospective study with a 10-year observation period and found a clinically significant decrease in PCS until the initial 2 years, but there were minimal changes thereafter (13).

Regarding urinary function, Koga *et al*. reported that urinary function assessed using EPIC did not return to baseline until 3 years after implantation (11). Sanda *et al*. also reported prolonged urinary obstruction and irritation symptoms, using EPIC (32). In this study, UCLA-PCI–assessed urinary function returned to baseline at 48 months. These differences may be influenced by the characteristics of the questionnaires. UCLA-PCI focuses primarily on urinary incontinence rather than obstructive or irritation symptoms, whereas EPIC is a comprehensive assessment that includes obstructive and irritating symptoms. Despite these limitations, considering the IPSS, the result of the UCLA-PCI was considered relatively well representative of urinary function in this study.

Concerning bowel function, Punenn *et al*., using UCLA-PCI and SF-8, also found that bowel function declined clinically early after implantation and worsened over time (13). Henderson *et al*. reported that the addition of EBRT to LDB was associated with a deteriorated bowel function (14). Koga *et al*. reported that bowel function was lower starting from 1 year in patients treated with combination therapy than in those treated with LDB alone (11). In this study, the bowel function in the overall cohort quickly returned to baseline after an early decline. In addition, there was no significant difference between the monotherapy and EBRT combination groups. To examine differences between this study and previous reports, it is necessary to compare the characteristics of the EBRT and the dose distribution of LDB. In this study, all cases of EBRT were treated with IMRT, which has the benefit of reduced bowel toxicity due to a narrowed irradiation field.

With respect to sexual function, Ferrer *et al*. reported that sexual function did not consistently deteriorate during the 2-year observation period (33). In contrast, Punenn *et al*. reported that there was a clinical decrease in sexual function for the first 2 years after implantation, but there was no clinical decrease 5-10 years thereafter. Roeloffzen *et al*. reported that although sexual function decreased early after implantation, it was relatively stable until up to 6 years from treatment (12). In this study, sexual function decreased early after implantation and then temporarily returned to baseline, although sexual function eventually decreased. Previous reports have identified age (12, 32), aging (13), higher baseline sexual function (13), and the addition of hormone therapy (12, 14) and EBRT (14) as clinical factors associated with a clinically significant decrease in sexual function after implantation.

In this study, multivariate analysis to identify predictive factors of a clinically significant decrease in sexual function at 24, 36, and 48 months identified a higher prostate V100 and baseline sexual function as predictors. Chasseray *et al*. reported that the radiation dose to the penile bulb and the prostate apex positioned closely to the penile bulb were associated with erectile dysfunction (34). Prostate V100 represents the percentage of the prostate that receives 100% of the prescribed dose. Radiation to the prostate, penile bulb, and other surrounding organs may be associated with decreased sexual function.

In this study, the sexual function did not return to baseline after an early deterioration, but the results that prostate V100 and baseline sexual function were predictive factors may be beneficial. Because identifying predictors may lead to a better understanding of the post-LDB course, particularly for patients with a high-level sexual function at baseline and for their partners. In addition, Prostate V100, which is usually assessed at the time of LDB, can be easily applied. To evaluate the usefulness of prostate V100, future studies should include the International Index of Erectile Function-5 (35) and investigation of the distribution in the radiation field.

This study has certain limitations. First, this was a single-centre retrospective study that included a small number of patients. Second, we used UCLA-PCI to assess disease-specific HRQOL, but UCLA-PCI cannot assess symptoms related to urinary irritation, obstruction, and hormone therapy compared to EPIC. Third, the median observation period was insufficient. Because PCA patients are projected to have long-term survival, further research on longitudinal changes in their HRQOL are needed based on the results of the present study. Despite these limitations, we believe that our study is valuable because the findings will be helpful to better understand the disease course after LDB.

In conclusion, most aspects of the HRQOL of PCA patients who undergo LDB returned to baseline after the early transient deterioration. These trends were similar between the LDB monotherapy and EBRT combination groups. The MCS showed an upward trend after treatment, while sexual function showed a downward trend. The prostate V100 and baseline UCLA-PCI sexual function scores predicted a clinical sexual deterioration in the late post-implantation period. These results may provide more accurate information for patients with preserved sexual function before treatment and for their partners.

Conflicts of Interest

The Authors declare that there are no conflicts of interest with regard to the present study.

Authors' Contributions

All Authors contributed to the study concept and design, analysis, and drafting of the manuscripts. All Authors read and approved the final version of the manuscript before submission.

Acknowledgements

The Authors thank M. Mori, H. Masuda, and Y. Morimatsu (Department of Environmental Medicine, Kurume University School of Medicine, Kurume, Japan) for their cooperation in creating this article.

References

1 Grimm P, Billiet I, Bostwick D, Dicker AP, Frank S, Immerzeel J, Keyes M, Kupelian P, Lee WR, Machtens S, Mayadev J, Moran BJ, Merrick G, Millar J, Roach M, Stock R, Shinohara K, Scholz M, Weber E, Zietman A, Zelefsky M, Wong J, Wentworth S, Vera R and Langley S: Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the prostate cancer results study

group. BJU Int *109(Suppl 1)*: 22-9, 2012. PMID: 22239226. DOI: 10.1111/j.1464-410X.2011.10827.x

2 Ito K, Saito S, Yorozu A, Kojima S, Kikuchi T, Higashide S, Aoki M, Koga H, Satoh T, Ohashi T, Nakamura K, Katayama N, Tanaka N, Nakano M, Shigematsu N, Dokiya T and Fukushima M: Nationwide Japanese prostate cancer outcome study of permanent iodine-125 seed implantation (J-POPS): first analysis on survival. Int J Clin Oncol *23(6)*: 1148-1159, 2018. PMID: 29934842. DOI: 10.1007/s10147-018-1309-0

3 Ohashi T, Yorozu A, Saito S, Tanaka N, Katayama N, Kojima S, Maruo S, Kikuchi T, Dokiya T, Fukushima M and Yamanaka H: Urinary and rectal toxicity profiles after permanent iodine-125 implant brachytherapy in Japanese men: Nationwide J-POPS multi-institutional prospective cohort study. Int J Radiat Oncol Biol Phys *93(1)*: 141-149, 2015. PMID: 26279031. DOI: 10.1016/j.ijrobp.2015.05.014

4 Tanaka N, Yorozu A, Kikuchi T, Higashide S, Kojima S, Ohashi T, Katayama N, Nakamura K, Saito S, Dokiya T and Fukushima M: Genitourinary toxicity after permanent iodine-125 seed implantation: The nationwide Japanese prostate cancer outcome study of permanent iodine-125 seed implantation (J-POPS). Brachytherapy *18(4)*: 484-492, 2019. PMID: 31072729. DOI: 10.1016/j.brachy.2019.03.007

5 Stone NN and Stock RG: Long-term urinary, sexual, and rectal morbidity in patients treated with iodine-125 prostate brachytherapy followed up for a minimum of 5 Years. Urology *69(2)*: 338-342, 2007. PMID: 17320674. DOI: 10.1016/j.urology.2006.10.001

6 Spratt DE, Soni PD, McLaughlin PW, Merrick GS, Stock RG, Blasko JC and Zelefsky MJ: American brachytherapy society task group report: Combination of brachytherapy and external beam radiation for high-risk prostate cancer. Brachytherapy *16(1)*: 1-12, 2017. PMID: 27771243. DOI: 10.1016/j.brachy.2016.09.006

7 Kee DLC, Gal J, Falk AT, Schiappa R, Chand ME, Gautier M, Doyen J and Hannoun-Levi JM: Brachytherapy *versus* external beam radiotherapy boost for prostate cancer: Systematic review with meta-analysis of randomized trials. Cancer Treat Rev *70*: 265-271, 2018. PMID: 30326422. DOI: 10.1016/j.ctrv.2018.10.004

8 Crook JM, Gomez-Iturriaga A, Wallace K, Ma C, Fung S, Alibhai S, Jewett M and Fleshner N: Comparison of health-related quality of life 5 years after SPIRIT: Surgical prostatectomy *versus* interstitial radiation intervention trial. J Clin Oncol *29(4)*: 362-8, 2011. PMID: 21149658. DOI: 10.1200/JCO.2010.31.7305

9 Lardas M, Liew M, van den Bergh RC, De Santis M, Bellmunt J, Van den Broeck T, Cornford P, Cumberbatch MG, Fossati N, Gross T, Henry AM, Bolla M, Briers E, Joniau S, Lam TB, Mason MD, Mottet N, van der Poel HG, Rouvière O, Schoots IG, Wiegel T, Willemse PPM, Yuan CY and Bourke L: Quality of life outcomes after primary treatment for clinically localised prostate cancer: A systematic review. Eur Urol *72(6)*: 869-885, 2017. PMID: 28757301. DOI: 10.1016/j.eururo.2017.06.035

10 Zelefsky MJ, Poon BY, Eastham J, Vickers A, Pei X and Scardino PT: Longitudinal assessment of quality of life after surgery, conformal brachytherapy, and intensity-modulated radiation therapy for prostate cancer. Radiother Oncol *118(1)*: 85-91, 2016. PMID: 26780999. DOI: 10.1016/j.radonc.2015.11.035

11 Koga H, Naito S, Ishiyama H, Yorozu A, Saito S, Kojima S, Higashide S, Kikuchi T, Nakamura K, Dokiya T and Fukushima M: Patient-reported health-related quality of life up to three years after the treatment with permanent brachytherapy: Outcome of the large-scale, prospective longitudinal study in Japanese prostate cancer outcome study by permanent I-125 seed implantation (J-POPS). Brachytherapy *18(6)*: 806-813, 2019. PMID: 31378511. DOI: 10.1016/j.brachy.2019.06.006

12 Roeloffzen EMA, Lips IM, van Gellekom MPR, van Roermund J, Frank SJ, Battermann JJ and van Vulpen M: Health-related quality of life up to six years after ^{125}I brachytherapy for early-stage prostate cancer. Int J Radiat Oncol Biol Phys *76(4)*: 1054-1060, 2010. PMID: 20097486. DOI: 10.1016/j.ijrobp.2009.03.045

13 Punnen S, Cowan JE, Chan JM, Carroll PR and Cooperberg MR: Long-term health-related quality of life after primary treatment for localized prostate cancer: Results from the CaPSURE registry. Eur Urol *68(4)*: 600-608, 2015. PMID: 25242555. DOI: 10.1016/j.eururo.2014.08.074

14 Henderson A, Laing RW and Langley SEM: Quality of life following treatment for early prostate cancer: Does low dose rate (LDR) brachytherapy offer a better outcome? A review. Eur Urol *45(2)*: 134-141, 2004. PMID: 14733996. DOI: 10.1016/j.eururo.2003.09.015

15 Davis BJ, Horwitz EM, Lee WR, Crook JM, Stock RG, Merrick GS, Butler WM, Grimm PD, Stone NN, Potters L, Zietman AL and Zelefsky MJ: American brachytherapy society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. Brachytherapy *11(1)*: 6-19, 2012. PMID: 22265434. DOI: 10.1016/j.brachy.2011.07.005

16 NCCN clinical practice guidelines in oncology prostate cancer version 2.2020: National Comprehensive Cancer Network® (NCCN®), 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf [Last accessed on 13 July 2020]

17 Becher E, Roehrborn CG, Siami P, Gagnier RP, Wilson TH and Montorsi F: The effects of dutasteride, tamsulosin, and the combination on storage and voiding in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the combination of avodart and tamsulosin study. Prostate Cancer Prostatic Dis *12(4)*: 369-374, 2009. PMID: 19901936. DOI: 10.1038/pcan.2009.37

18 Iinuma K, Nakano M, Kato T, Kato D, Takai M, Maekawa YM, Nakane K, Mizutani K, Tsuchiya T, Ishihara T, Ito M, Matsuo M and Koie T: Assessment of long-term changes in lower urinary tract symptoms in patients with prostate cancer who underwent low-dose-rate prostate brachytherapy. Urology *142*: 213-220, 2020. PMID: 32416115. DOI: 10.1016/j.urology.2020.04.106

19 Fukuhara S and Suzukamo Y: Manual of the SF-8 Japanese version. Fukuhara S and Suzukamo Y (eds.). Kyoto, Institute for Health Outcome and Process Evaluation Research, 2004.

20 Sugimoto M, Takegami M, Suzukamo Y, Fukuhara S and Kakehi Y: Health-related quality of life in Japanese men with localized prostate cancer: Assessment with the SF-8. Int J Urol *15(6)*: 524-528, 2008. PMID: 18422571. DOI: 10.1111/j.1442-2042.2008.02046.x

21 Litwin MS, Hays RD, Fink A, Ganz PA, Leake B and Brook RH: The UCLA prostate cancer index: Development, reliability, and validity of a health-related quality of life measure. Med Care *36(7)*: 1002-1012, 1998. PMID: 9674618. DOI: 10.1097/00005650-199807000-00007

22 Suzukamo Y, Kakehi Y, Kamoto T, Arai Y, Ogawa O and Fukuhara S: Translation and adaptation of the UCLA prostate cancer index for use in Japan. Nihon Hinyokika Gakkai Zasshi *93(6)*: 659-668, 2002. PMID: 12385090. DOI: 10.5980/jpnjurol1989.93.659

23 Norman GR, Sloan JA and Wyrwich KW: Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. Med Care *41(5)*: 582-592, 2003. PMID: 12719681. DOI: 10.1097/01.MLR.0000062554.74615.4C

24 Charlson M, Szatrowski TP, Peterson J and Gold J: Validation of a combined comorbidity index. J Clin Epidemiol *47(11)*: 1245-1251, 1994. PMID: 7722560. DOI: 10.1016/0895-4356(94)90129-5.

25 Cesaretti JA, Stone NN and Stock RG: Urinary symptom flare following I-125 prostate brachytherapy. Int J Radiat Oncol Biol Phys *56(4)*: 1085-1092, 2003. PMID: 12829146. DOI: 10.1016/S0360-3016(03)00210-4

26 Lehrer S, Cesaretti J, Stone NN and Stock RG: Urinary symptom flare after brachytherapy for prostate cancer is associated with erectile dysfunction and more urinary symptoms before implantation. BJU Int *98(5)*: 979-981, 2006. PMID: 17034599. DOI: 10.1111/j.1464-410X.2006.06398.x

27 Keyes M, Miller S, Moravan V, Pickles T, Liu M, Spadinger I, Lapointe V and Morris WJ: Urinary symptom flare in 712 ^{125}I prostate brachytherapy patients: Long-term follow-up. Int J Radiat Oncol Biol Phys *75(3)*: 649-655, 2009. PMID: 19211199. DOI: 10.1016/j.ijrobp.2008.11.043

28 Eriguchi T, Yorozu A, Kuroiwa N, Yagi Y, Nishiyama T, Saito S, Toya K, Hanada T, Shiraishi Y, Ohashi T and Shigematsu N: Predictive factors for urinary toxicity after iodine-125 prostate brachytherapy with or without supplemental external beam radiotherapy. Brachytherapy *15(3)*: 288-295, 2016. PMID: 26924022. DOI: 10.1016/j.brachy.2015.12.011

29 Onishi K, Tanaka N, Miyake M, Nakai Y, Anai S, Torimoto K, Yamaki K, Asakawa I, Hasegawa M, Fujii T, Konishi N and Fujimoto K: Changes in lower urinary tract symptoms after iodine-125 brachytherapy for prostate cancer. Clin Transl Radiat Oncol *14*: 51-58, 2019. PMID: 30547097. DOI: 10.1016/j.ctro.2018.11.001

30 Jacobs BL, Smith RP, Beriwal S and Benoit RM: Changes in lower urinary tract symptoms after prostate brachytherapy. J Contemp Brachytherapy *3(3)*: 115-120, 2011. PMID: 23346119. DOI: 10.5114/jcb.2011.24816

31 Mols F, van de Poll-Franse LV, Vingerhoets AJJM, Hendrikx A, Aaronson NK, Houterman S, Coebergh JWW and Essink-Bot ML: Long-term quality of life among Dutch prostate cancer survivors: Results of a population-based study. Cancer *107(9)*: 2186-2196, 2006. PMID: 17013914. DOI: 10.1002/cncr.22231

32 Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, Lin X, Greenfield TK, Litwin MS, Saigal CS, Mahadevan A, Klein E, Kibel A, Pisters LL, Kuban D, Kaplan I, Wood D, Ciezki J, Shah N and Wei JT: Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med *358(12)*: 1250-1261, 2008. PMID: 18354103. DOI: 10.1056/NEJMoa074311

33 Ferrer M, Suárez JF, Guedea F, Fernández P, Macías V, Mariño A, Hervas A, Herruzo I, Ortiz MJ, Villavicencio H, Craven-Bratle J, Garin O and Aguiló F: Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys *72(2)*: 421-432, 2008. PMID: 18325680. DOI: 10.1016/j.ijrobp.2007.12.024

34 Chasseray M, Dissaux G, Bourbonne V, Boussion N, Goasduff G, Malloreau J, Malhaire JP, Fournier G, Tissot V, Pradier O, Valeri A and Schick U: Dose to the penile bulb and individual patient anatomy are predictive of erectile dysfunction in men treated with ^{125}I low dose rate brachytherapy for localized prostate cancer. Acta Oncol *58(7)*: 1029-1035, 2019. PMID: 30761939. DOI: 10.1080/0284186X.2019.1574981

35 Rosen RC, Cappelleri JC, Smith MD, Lipsky J and Peña BM: Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res *11(6)*: 319-326, 1999. PMID: 10637462. DOI: 10.1038/sj.ijir.3900472

Received August 22, 2020
Revised September 6, 2020
Accepted September 10, 2020