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Abstract

Background: The relationship between the grading of toxicities based on toxicity criteria and longitudinal changes in quality of life (QOL) scores after permanent prostate brachytherapy (PPB) for localized prostate cancer remains unclear. This study aimed to evaluate these relationships.

Materials and methods: We assessed 107 patients treated with PPB using Iodine-125 alone from May 2007 to April 2010. Disease-specific QOL scores before PPB and at 1, 3, 6, 12, and 24 months after PPB were retrospectively evaluated with the Expanded Prostate Cancer Index Composite (EPIC), focusing on urinary domains. Toxicities were graded using the Radiation therapy oncology group and the European organization for research and treatment of cancer toxicity criteria.

Results: The median follow-up duration was 116 (range 18–148) months. Thirty-four patients (31.8%) developed grade ≥ 2 acute genitourinary (GU) toxicities; six (5.6%) developed grade ≥ 2 late GU toxicities. The general urinary domain score dropped significantly at 1 month (77.1 ± 14.1) post-PPB compared to the baseline score (92.2 ± 8.2), and then gradually returned to the baseline level by 12 months (93.7 ± 8.3) post-PPB. Reductions in the general urinary domain scores, including its subscale scores at 1, 3, and 6-months post-PPB were significantly greater among patients with grade ≥ 2 GU toxicity than among those with grade 0–1 GU toxicity. Changes in urinary domain scores demonstrated a close relationship with acute GU toxicity grades after PPB.

Conclusions: Longitudinal assessments of the EPIC QOL scores provided additional information regarding time-course changes in GU toxicities after PPB.

Key words: I-125 brachytherapy; quality of life; genitourinary toxicity; dose-volume histogram parameter; prostate cancer; radiotherapy

Introduction

Permanent prostate brachytherapy (PPB) using I-125 or Pd-103 is an established radical treatment for localized prostate cancer, yielding excellent local control and long-term biochemical control [1–4]. In recent years, PPB has been reported to have good outcomes as a treatment for locally recurrent prostate cancer [5, 6]. Like external beam radiation therapy (EBRT), including three-dimensional conformal radiation therapy and intensity-modulated radiation therapy, dose escalation improves the clinical outcomes of PPB. Stock et al. [7] reported that freedom from prostate-specific antigen failure at 10 years was closely associated with the biologically effective dose, which was the most significant predictor of positive post-treatment biopsy results. However, toxicity also increased as the total delivered dose increased. The incidence of acute genitourinary (GU) toxicity of grade ≥ 2 after PPB monotherapy ranges from 10% to 40% [8–10], and acute urinary retention (AUR) occurs in 5–15% of patients [12–15]. Kittel et al. [3] studied the long-term toxicity of PPB for prostate cancer and reported that the overall rates of late GU and gastrointestinal toxicities of grade ≥ 3 were 7.6% and 0.8%, respectively, and that age ≥ 70 years and prostate length ≥ 5 cm were predictive of grade ≥ 3 toxicity. As described above, the incidence and severity of toxicity after PPB differs greatly among reports partly due to the difference in techniques, including the prescribed dose, seed placement, or treatment quality. However, the profiles of acute genitourinary (GU) toxicity caused by PPB may not be the same as those caused by EBRT because the incidence of AUR after PPB is higher than that after EBRT. Treatment-related toxicity has been assessed based on toxicity grading using standardized toxicity criteria, such as the Radiation Therapy Oncology Group and the

European Organization for Research and Treatment of Cancer (RTOG/EORTC) toxicity criteria [16] or Common Terminology Criteria for Adverse Events. When grading toxicity, the worst symptom that occurs after treatment is considered. It can be classified as acute or late, depending on the interval between treatment completion and its occurrence. In other words, toxicity grading does not consider its duration or recovery. Another approach for assessing the severity of symptoms is to evaluate the quality of life (QOL). The severity of treatment toxicities can be well assessed by evaluating QOL using standardized self-administered questionnaires. Among the existing methods of QOL evaluation, longitudinal assessments of QOL before and after treatment have the potential to provide important information regarding the duration of and recovery from toxicities as well as the toxicity severity. To the best of our knowledge, few studies have reported a relationship between the grading of toxicities based on toxicity criteria and the longitudinal changes in the QOL score after PPB for localized prostate cancer. In this study, we used the Expanded Prostate Cancer Index Composite (EPIC) Japanese version [17] as a proxy for disease specific QOL. The EPIC comprises four separate domains (urinary, bowel, sexual, and hormonal); however, we mainly focused on the relationship between changes in the urinary domain, including its subscales, and the GU toxicity grade after PPB. Prior studies have reported on the relationship between changes in the disease-specific QOL score, as assessed with the EPIC, and the grading of GU toxicity after high-dose rate brachytherapy with EBRT [18] and intermediate hypofractionated intensity-modulated radiation therapy (66 Gy in 22 fractions, 3 fractions per week) [19] for localized prostate cancer. Herein, we evaluated the relationship between changes in disease-specific QOL scores and GU toxicity grade

after PPB using I-125 alone for localized prostate cancer to clarify the usefulness of the disease-specific QOL in assessing treatment-related toxicity.

Materials and methods

Patients

The study was conducted between May 2007 and April 2010 among patients with localized prostate cancer (T1-3N0M0) treated with PPB alone using I-125 at our institution. We assessed 107 consecutive patients whose disease specific QOL was evaluated before PPB and at 1, 3, 6, 12, and 24 months after PPB and who had been followed up for ≥ 12 months. The clinical risk group was defined using the D'Amico risk classification [20]. Generally, androgen-deprivation therapy (ADT) was administered according to the risk classification as follows: no ADT to patients in the low-risk group, 4–6 months neoadjuvant ADT to those in the intermediate-risk group, and 4–6 months neoadjuvant ADT and 6 months adjuvant ADT to those in the high-risk group. ADT mainly comprised administration of a luteinizing hormone-releasing hormone agonist plus a nonsteroidal or steroidal antiandrogen. Patients with gland sizes of ≥ 50 cm^3 (including those with low-risk disease) received short-term (3–4 months) neoadjuvant ADT to achieve prostate volume reduction before PPB. Patients with a large substance defect after transurethral resection were excluded from this study. All study participants provided written informed consent, and the study protocol was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the institutional ethics review board.

PPB

PPB comprised transperineal implantation with I-125 seeds as monotherapy in all patients. The procedure of PPB was conducted with an online intra-operative planning technique using the SPOT system (Nucletron BV, Veenendaal, The Netherlands). Under general anesthesia in lithotomy position, images of transrectal ultrasonography (TRUS) were acquired and the entire prostate gland, prostatic urethra and rectum were delineated on 1-mm slices. A planned prescribed dose of 144 Gy was used according to the TG-43 protocol of the American Association of Physicists in Medicine guidelines [21]. The criteria for intraoperative planning were as follows: the percentage of the prostate volume receiving the prescribed dose of 144 Gy was > 95%, that receiving 150% of the prescribed dose was < 65%, and the dose delivered to 90% of the prostate (D90) was > 160 Gy. Under the guidance of the intra-operative planning, the needles were inserted transperineally under TRUS, and then seeds (single) were inserted into optimal position using Mick Applicator. Just after implantation, a TRUS was performed to check the leakage of seeds, and 1 month later, computed tomography (CT) was performed for post-plan. If an inadequate dose was found, no further boost was added.

Follow-up and evaluation of toxicities

Toxicities were evaluated at every visit, and all patients were followed up at 1–3-month intervals. Toxicity caused by PPB were scored among all patients based on the severity of symptoms during the follow-up period, and the toxicity were graded based on the RTOG/EORTC toxicity criteria [16]. Each symptom was given a grade from 0 (no

symptoms) to 5 (death directly related to radiation effects). Acute toxicity was that evaluated within 6 months after PPB completion and late toxicities were those evaluated thereafter.

Longitudinal QOL evaluation

Longitudinal disease-specific health-related QOL was prospectively evaluated just before PPB and at 1, 3, 6, 12, and 24 months after PPB using the EPIC Japanese version [17] to assess the time-course changes and recovery patterns of toxicities. The EPIC comprised a 50-item questionnaire that quantified the patient's prostate cancer-specific QOL in four separate domains (urinary, bowel, sexual, and hormonal domains). The urinary domain consisted of four subscales (urinary function, urinary bother, urinary irritation, and urinary incontinence) and the bowel, sexual, and hormonal domains each comprised two subscales (function and bother).

Statistical analysis

The patients' characteristics are expressed as medians and ranges for continuous variables, and percentages for categorical variables. The clinical and dosimetric factors according to GU toxicity grade (Grade 0–1 vs. Grade 2–3) are expressed as average and standard deviation. The difference in the average value of the EPIC QOL score at each observation time point was tested using a one-way repeated analysis of variance (ANOVA) for all patients, and two-way repeated ANOVA for two groups (Grade 0–1 vs. Grade 2–3). Comparative analyses between two groups (Grade 0-1 vs. Grade 2-3) were

performed with unpaired two-tailed *t*-tests. All statistical analyses were performed using Microsoft® Excel for Mac version 16.26 (Microsoft Corporation, Redmond, WA, USA). In all statistical analyses, $p < 0.05$ was considered reflective of statistical significance.

Results

Patients

The median follow-up duration after completing PPB was 116 (range 18–148) months. The characteristics of the patients/tumors are shown in Table 1. The risk groups were distributed as follows: 52 patients in the low-risk group (49%), 47 patients in the intermediate-risk group (44%), and 8 patients in the high-risk group (7%). Among all the patients, 61 (57%) received neoadjuvant therapy and/or ADT.

Acute and late toxicity based on the RTOG/EORTC criteria

Acute GU toxicity scores were grade 0–1 for 73 patients (68.2%), grade 2 for 27 patients (25.2%), and grade 3 for 7 patients (6.6%). Late GU toxicity scores were grade 0–1 for 101 patients (94.4%) and grade 2 for 6 patients (5.6%). Regarding grade 3 acute GU toxicity, five patients experienced nocturia hourly or less frequently after PPB, but these symptoms resolved gradually after completing PPB with transient administration of an α1 blocker. Two patients developed urinary retention within 1 week after PPB but recovered within 1 week after transient placement of a urinary catheter. None of the patients experienced grade 4 acute GU toxicity. Regarding late GU toxicity, none of the patients experienced grade ≥ 3 toxicity during the entire observation period. Regarding

acute and late gastrointestinal toxicities, none of the patients experienced grade ≥ 2 toxicity during the entire observation period.

Clinical and dosimetric factors according to acute GU toxicity grade (grade 0–1 vs. grade 2–3)

We investigated clinical and dosimetric factors, including the number of inserted seeds, prostate volume at post-implant dosimetry, and dose-volume histogram parameters, such as prostatic D90, V100, and V150, plus D5 and D30 of the prostatic urethra, to clarify factors associated with the occurrence of grade 2–3 acute GU toxicities. Table 2 summarizes the average and standard deviation values of these factors among all patients; those with grade 0–1, and grade 2–3 acute GU toxicities. As shown in Table 2, there were no significant differences in these values between patients with grade 0–1, and grade 2–3 acute GU toxicity.

Changes in the EPIC QOL scores of the general urinary domain and its subscales

EPIC QOL scores of all domains were linearly transformed to a scale of 0 (lowest) to 100 (highest), whereby higher domain scores (range 0–100) represented better functioning and QOL. EPIC QOL scores were evaluated as average values with standard deviations at each point. Figure 1 shows the results of the changes in all domains among all the patients. The urinary (Fig. 1A) and bowel domains (Fig. 1B) exhibited significant differences (both $p < 0.01$) among the observation time points. The sexual (Fig. 1C; $p = 0.08$) and hormonal (Fig. 1D; $p = 0.38$) domains did not show significant differences among the observation time points. Regarding the urinary domain, the general urinary domain score dropped significantly at 1 month (77.1 ± 14.1)

after PPB completion as compared to the baseline score (92.2 ± 8.2) ($p < 0.01$), and then returned gradually to the baseline value by 12 months (92.0 ± 9.6) after PPB completion (Fig. 1A). The baseline general urinary domain score and the scores at 3 and 6 months after PPB were significantly different, indicating that significant reductions in the EPIC QOL general urinary domain score continued until 6 months after PPB. Regarding the subscales of the urinary domain, the changes in the scores of all subscales, including function, bother, irritation, and incontinence, showed similar trends as those observed in the general urinary domain scores, indicating that the baseline subscale scores and those obtained at 1, 3, and 6 months after PPB were significantly different (all $p < 0.01$) (Fig. 2).

Relationship between changes in the EPIC QOL scores of the general urinary domain and its subscales and GU toxicity grade

To evaluate the effects of the GU toxicity severity on the longitudinal changes in EPIC QOL scores, we investigated the relationship between the changes in the scores of the general urinary domain and its subscales and the GU toxicity grade by stratifying patients according to GU toxicity grade (i.e., patients with grade 0–1 and grade 2–3 toxicities).

Figures 3 and 4 show changes in the general urinary domain and its subscale scores according to the acute and late GU toxicity grades, respectively. Reduction in the general urinary domain score after PPB was observed in patients with both grade 0–1 and grade 2–3 acute GU toxicities. However, the reduction was more prominent among patients with grade 2–3 acute GU toxicity than among those with grade 0–1 acute GU toxicity (Fig. 3A). The differences in the general urinary domain scores at 1 and 3

months after PPB between patients with grade 0–1 and grade 2–3 acute toxicity were significant (all $p < 0.01$). Regarding the scores of the general urinary domain subscales, all subscale scores exhibited trends like those of the general urinary domain score (Fig. 3B–E). The differences in the scores of all subscales at 1 month after PPB between patients with grade 0–1 and grade 2–3 acute toxicity was significant (all $p < 0.01$); however, the duration of the reduction in QOL scores differed according to the subscale. The significant reduction in the urinary irritation QOL score recovered faster than did the reductions in the other subscale scores, and the reductions in the urinary bother and function subscale scores continued until 6 months after PPB. Among the subscales, the reductions in the urinary incontinence score among patients with grade 2–3 acute toxicity at 1 and 3 months after PPB were remarkable, indicating that the urinary incontinence score was the most susceptible to PPB among the subscale scores investigated, and that the urinary incontinence score persisted for a long time compared to other subscale scores. There were no significant differences in QOL scores between patients with grade 0–1 and grade 2 late GU toxicities (Fig. 4).

Discussion

The EPIC QOL scores of 107 consecutive patients treated with PPB alone showed that the general urinary domain score significantly decreased at 1 month after PPB completion as compared to the baseline score and then returned gradually to the baseline level. Concerning the QOL survey using the EPIC, a prospective study by Ash et al. [22] examining long-term OL after PPB using I-125 for localized prostate cancer demonstrated that the general urinary domain score fell to 69.3 at 6 weeks after PPB and returned to the pre-treatment level by 1-year post-treatment. In that study, the change in

the general urinary domain score with time mirrored the change in the International Prostate Symptom Score. The pattern of change in the urinary scores in the prior study was almost the same as the pattern observed in the present study. Among the subscales, Ash et al. [22] also demonstrated that urinary bother and irritation scores were mostly affected by PPB. Changes in the subscale scores of this study showed similar trends, with the reductions in the urinary bother and irritation subscale scores being greater than the reductions in the other subscale scores. Besides longitudinal changes among all patients, the results of this study demonstrated that the reductions in the scores for the general urinary domain and its subscales exhibited a close relationship with the acute GU toxicity grade. Regarding the subscales, the reductions in the urinary irritation scores recovered faster than did the reductions in the other subscale scores; the urinary continence score was the most susceptible to PPB among the subscale scores evaluated, and the influence of PPB on urinary continence persisted for a longer period than it did for the other subscale scores. To the best of our knowledge, this study is the first to demonstrate a close relationship between the EPIC scores for the general urinary domain and its subscales and the GU toxicity grade.

Herein, the toxicity severity could be evaluated using QOL assessments because the QOL scores of all domains were linearly transformed to a scale of 0 to 100. Moreover, longitudinal QOL assessments before and after treatment provided valuable information regarding the persistence of and recovery from treatment-related symptoms. Especially, the EPIC was useful for performing detailed evaluations of symptoms that were susceptible to treatment because the urinary domain comprised four subscales (function,

bother, irritation, and incontinence), and the changes in treatment-related symptoms could be evaluated according to each subscale.

Urinary toxicity profiles due to treatment may differ between EBRT and PPB; hence, detailed analyses of the changes in QOL scores that occur with each treatment may be an effective tool for exploring specific treatment-related morbidity and may provide information for improving treatment quality. Ávila et al. [23] reviewed patient-reported outcomes after treatment for clinically localized prostate cancer and mentioned that small deteriorations in urinary incontinence, irritative and obstructive symptoms, sexual function, and bowel bother were observed in meta-analyses of patients who underwent brachytherapy. Pinkawa et al. [24] compared EPIC QOL scores after PPB using I-125 and EBRT (70.2–72.0 Gy) for prostate cancer and demonstrated that the decreases in urinary function and bother scores were significantly greater after PPB than after EBRT at both 1 and 16 months, although bowel function/bother scores tended to be higher after PPB than after EBRT. Several studies proposed various clinical and dosimetric factors that may affect disease specific QOL after PPB. Using the cancer specific EORTC core questionnaire, Van Gellekom et al. [25] reported that D90 and prostate volume significantly affected the urinary symptom score. Concerning dosimetric factors, Vordermark et al. [26] analyzed longitudinal changes in QOL after PPB and reported that prostatic V150 was the only implant parameter significantly associated with both urinary and bowel symptoms at 4 weeks and 1-year post-treatment. In our analysis of all patients, we did not identify any significant dosimetric factors that influenced the reduction in QOL score and the occurrence of grade 2–3 acute GU toxicity. However, the general urinary domain score at baseline for all patients also

differed. This implies that pre-treatment urinary symptoms may affect changes in treatment-related urinary symptoms and QOL, although the scores for the general urinary domain and its subscales at baseline did not differ, even after stratification according to acute GU toxicity grade or prostate volume. Roeloffzen et al. [27] evaluated the effects of AUR among patients treated with PPB using I-125 on short- and long-term QOL, as assessed by the EORTC QLQ-PR25. The authors reported that patients with AUR had a significantly worse urinary QOL at all time points than did patients without AUR [25]. They also demonstrated that the pre-treatment International Prostate Symptom Score and neoadjuvant ADT were predictors of AUR, but the pre-treatment QOL did not have an added predictive value for changes in QOL. Assessing disease-specific and health-related QOL may also be useful for evaluating long-term changes in treatment-related symptoms. Roeloffzen et al. [28] reported patients' prospective health-related QOL for up to 6 years after PPB and concluded that the health-related QOL at 6 years after PPB did not significantly differ from that at baseline, although a significant deterioration in health-related QOL at 6 years was observed for urinary symptoms, bowel symptoms, pain, physical functioning, and sexual activity. Long-term assessments of QOL, especially disease-specific QOL, may clarify time-course changes in late toxicities in addition to acute toxicities; hence, comparing baseline QOL scores to QOL scores at 5–6 years after treatment may provide valuable information regarding the long-term positive and negative effects of QOL on treatment-related symptoms. Further research is needed to ensure the validity of longitudinal evaluations of EPIC QOL scores for the precise assessment of treatment-related symptoms after PPB.

Limitations of our study include its retrospective nature. As such, despite the long follow-up period, data for EPIC QOL scores at > 24 months post-treatment were unavailable. Furthermore, our sample size was relatively low; therefore, we were unable to draw a relationship between EPIC QOL scores and dose-volume histogram parameters of PPB and late toxicities.

To conclude, this study revealed that the changes in the urinary domain EPIC QOL scores, including the scores for all subscales, demonstrated a close relationship with the acute GU toxicity grade after PPB. Furthermore, longitudinal assessments of EPIC QOL scores provided additional information regarding time-course changes in acute toxicity after PPB. Our results suggest that longitudinal evaluations of EPIC QOL scores may be a useful tool for assessing the quality of prostate cancer treatment.

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Conflict of interest

None declared.

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Table 1. Characteristics of the patients and tumors

Variable	**No. of patients**	**Value(s)** **Median (Range)**	**% of patients**
Age [y]		71 (52–80)	
ADT			
Yes	61		57.0
No	46		43.0
T stage			
T1c–T2a	100		93.5
T2b	5		4.7
T2c–T3b	2		1.8
Gleason score			
5–6	62		57.9

7	38		35.5
8–9	7		6.6
PSA [ng/mL]		**7.1 (3.2–21.9)**	
≤ 10	95		58.5
10–20	11		21.0
> 20	1		20.5
Risk distribution			
Low-risk	52		
Intermediate-risk	74		
High-risk	8		

ADT — androgen-deprivation therapy; PSA — prostate specific antygen

Table 2. Clinical and dosimetric factors according to genitourinary (GU) toxicity grade. There were no significant differences in any of the factors analyzed between patients with grade 0–1 acute GU toxicity and those with grade 2–3 acute GU toxicity

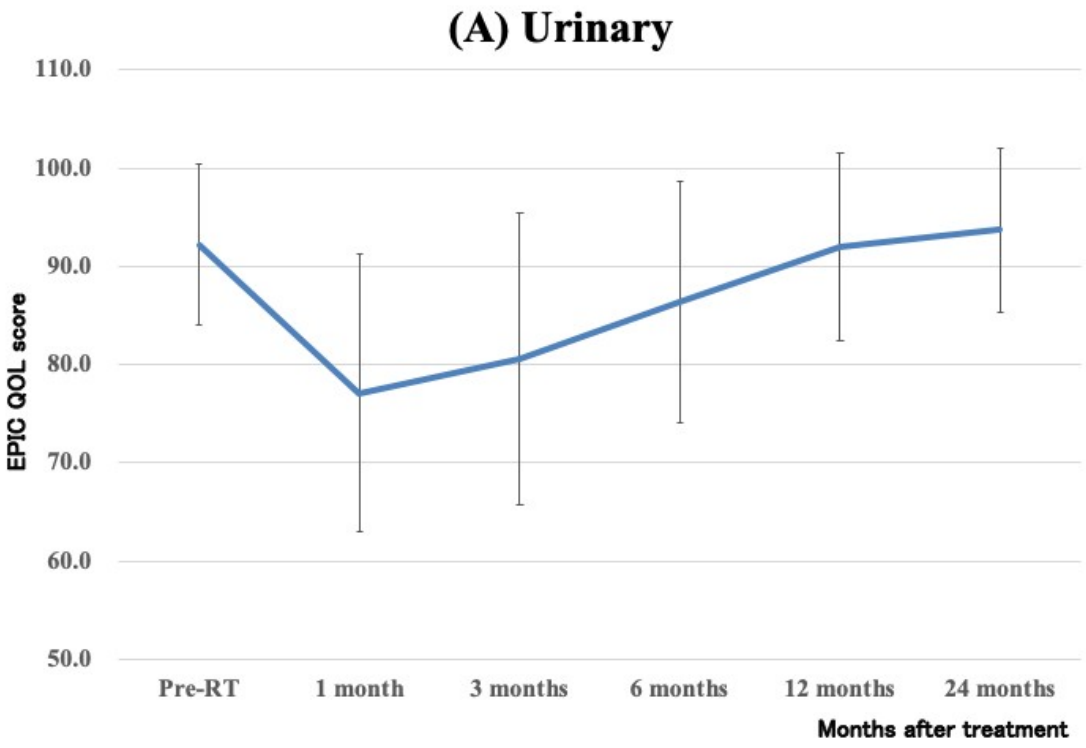
Variables	**Grade 0–1**	**Grade 2–3**	**p-value**
Number of seeds	69.5 ± 15.4	68.9 ± 16.1	0.82
Prostate volume [cc]	24.0 ± 8.6	25.3 ± 9.8	0.47
Prostate_D90 [Gy]	165.5 ± 15.6	161.1 ± 16.5	0.18
Prostate_V100 (%)	95.6 ± 3.3	93.9 ± 7.8	0.10
Prostate_V150 (%)	61.2 ± 12.7	57.7 ± 13.0	0.19
Urethra_D5 [Gy]	215.7 ± 36.5	205.9 ± 33.4	0.19
Urethra_D30 [Gy]	195.7 ± 26.6	189.1 ± 28.3	0.24

Table 3. Number of acute and late toxicities scored according to the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC)

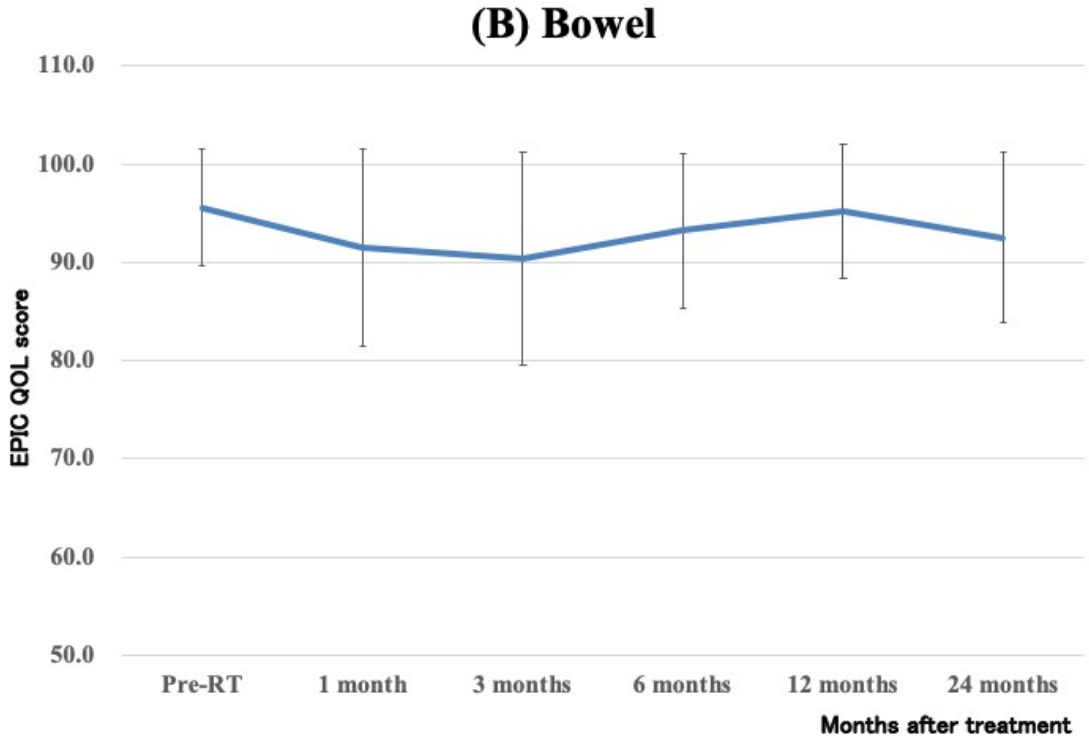
Toxicity	**Grade 0–1**	**Grade 2**	**Grade 3**
Acute			

Genitourinary	73 (68.2%)	27 (25.2%)	7 (6.6%)
Gastrointestinal	107 (100%)	0 (0%)	0 (0%)
Late			
Genitourinary	101 (94.4%)	6 (5.6%)	0 (0%)
Gastrointestinal	107 (100%)	0 (0%)	0 (0%)

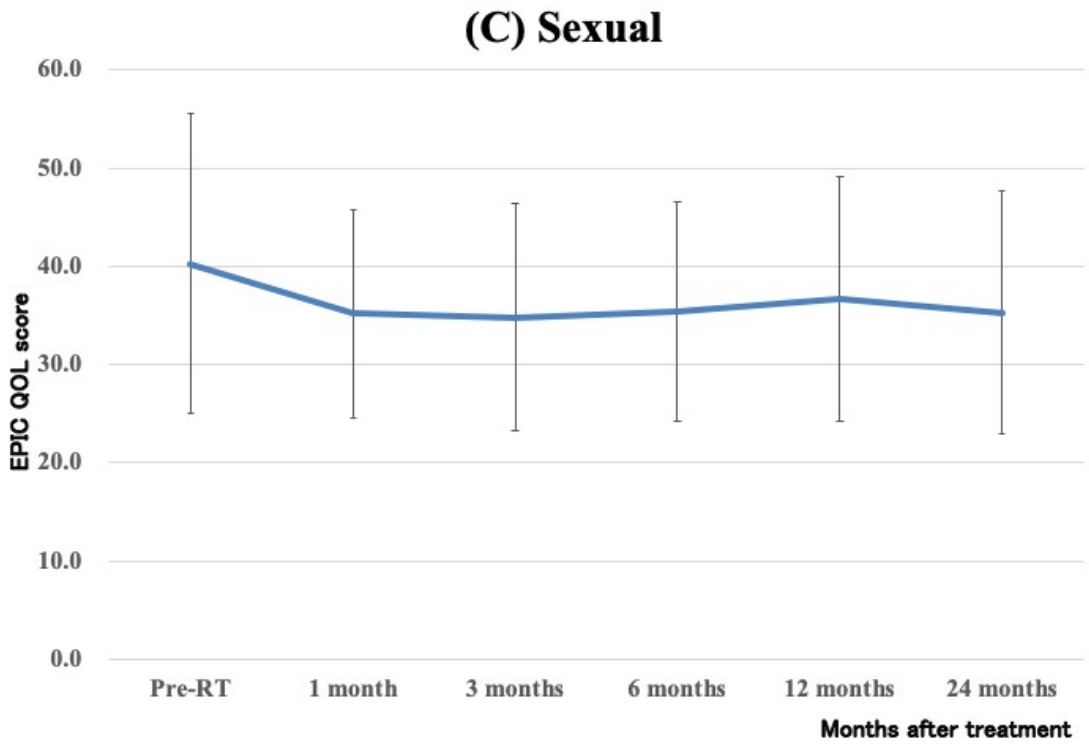
Figure 1. Longitudinal changes in the Expanded Prostate Cancer Index Composite quality of life (EPIC QOL) scores among all patients. Changes in the following general domains are shown: (a) urinary, (b) bowel, (c) sexual, and (d) hormonal.



All patients	92.2 ± 8.2	77.1 ± 14.1	80.6 ± 14.8	86.4 ± 12.3	92.0 ± 9.6	93.7 ± 8.3



All patients	95.6 ± 5.9	91.5 ± 10.0	90.4 ± 10.8	93.2 ± 7.8	95.2 ± 6.9	92.5 ± 8.7



	Pre-RT	1 month	3 months	6 months	12 months	24 months
All patients	40.3 ± 15.3	35.2 ± 10.6	34.8 ± 11.6	35.4 ± 11.2	36.7 ± 12.4	35.3 ± 12.4

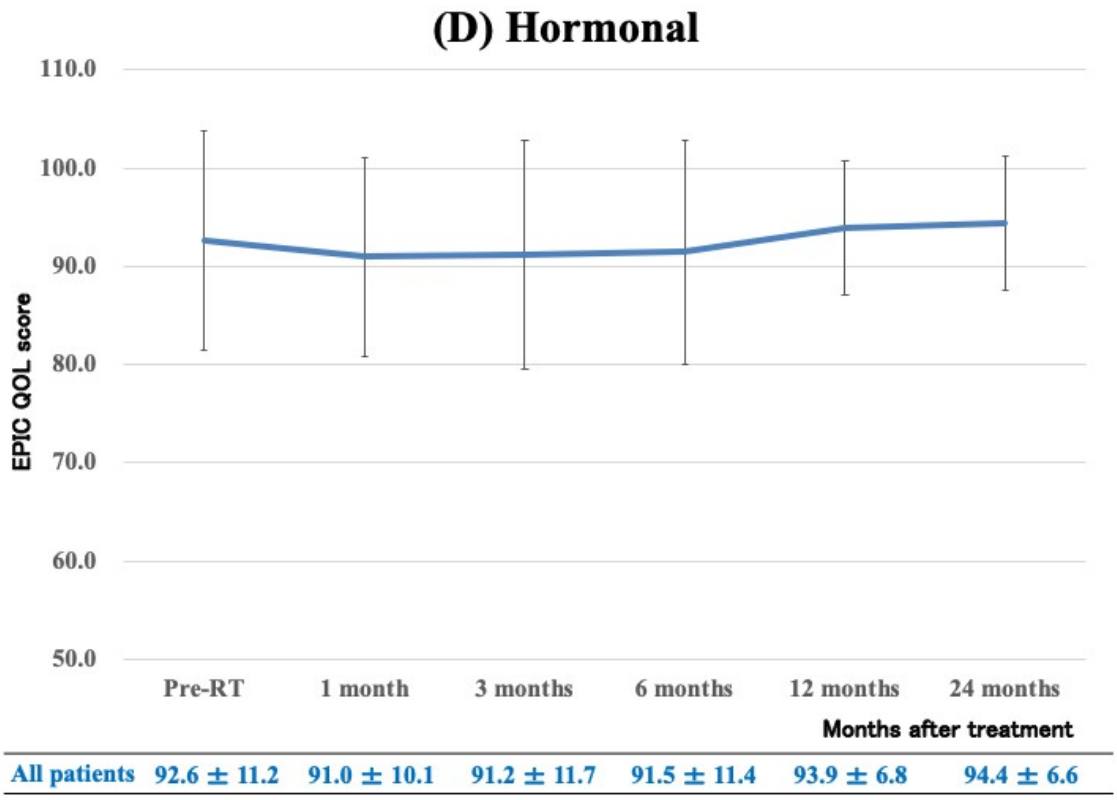
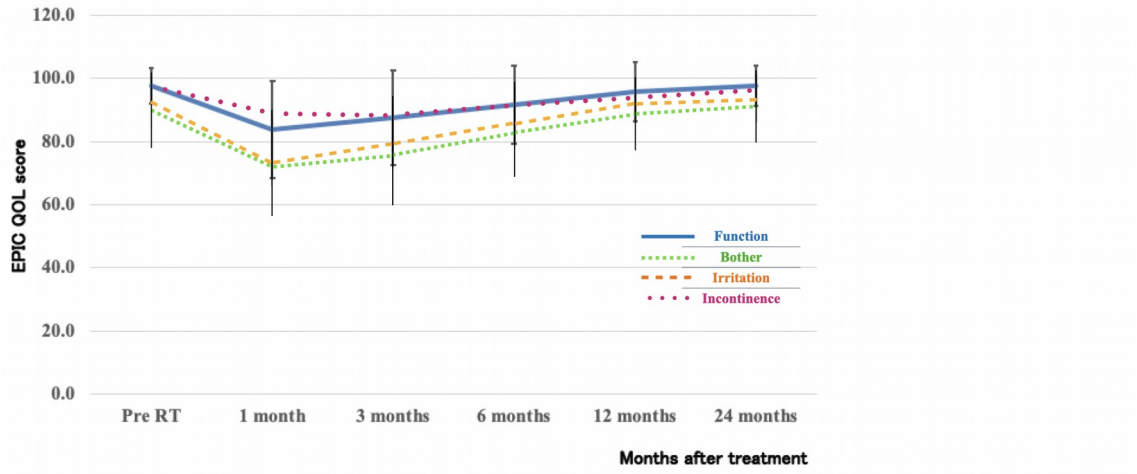
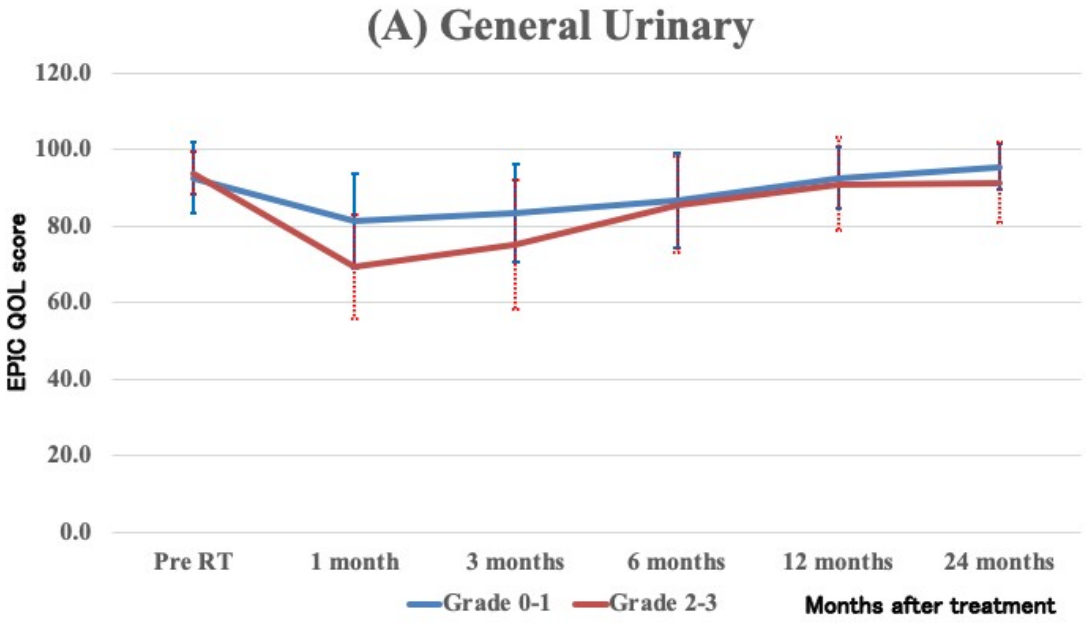


Figure 2. Longitudinal changes in the Expanded Prostate Cancer Index Composite quality of life (EPIC QOL) scores among all patients. Changes in the following urinary subscales are shown: function, bother, irritation, and incontinence.

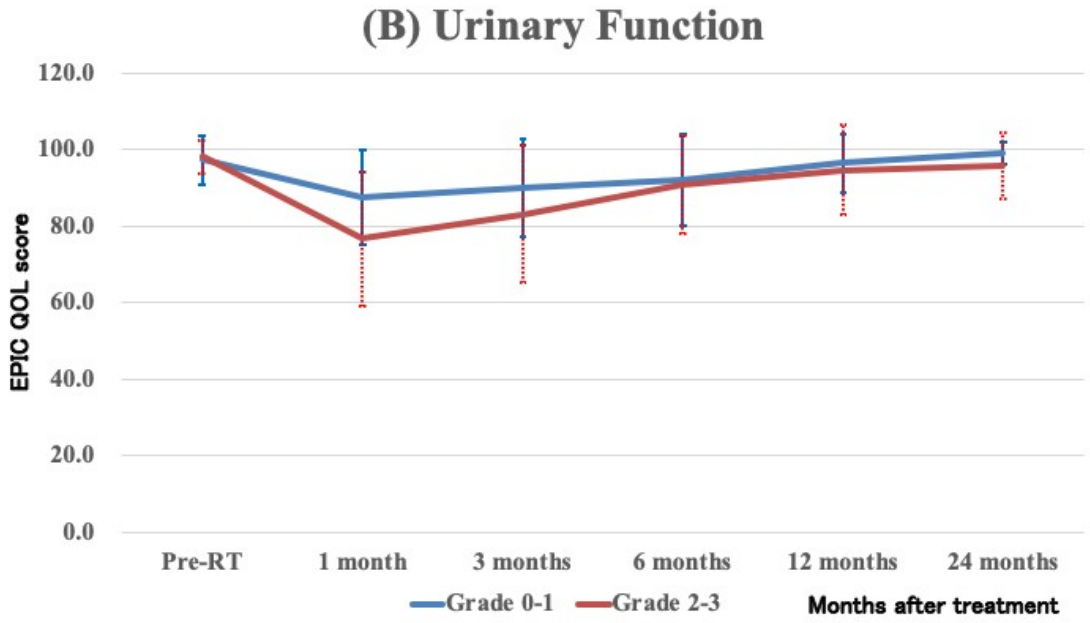


Function	97.5 ± 5.7	83.7 ± 15.3	87.9 ± 15.0	91.6 ± 12.3	95.8 ± 9.2	97.6 ± 6.2
Bother	89.6 ± 11.3	72.3 ± 16.2	75.5 ± 16.3	82.7 ± 14.1	88.6 ± 11.5	90.8 ± 11.1
Irritation	92.4 ± 9.3	73.4 ± 16.8	79.2 ± 15.4	85.5 ± 13.7	92.1 ± 8.8	93.5 ± 7.7
Incontinence	97.1 ± 7.1	88.8 ± 18.5	88.3 ± 18.5	91.4 ± 12.8	93.8 ± 14.5	96.0 ± 10.1

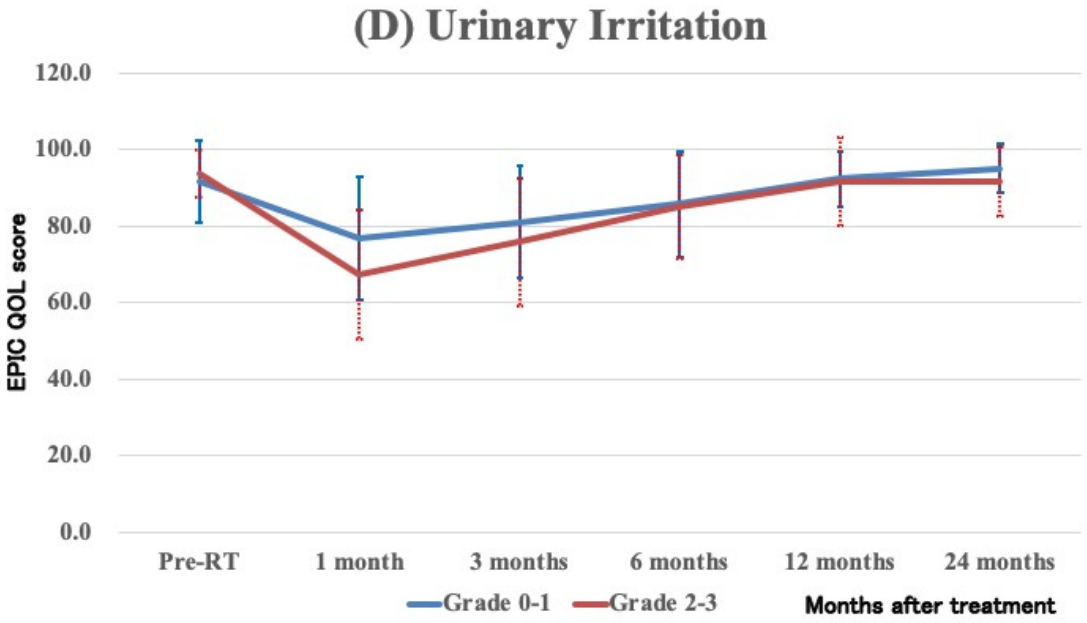
Figure 3. Longitudinal changes in the Expanded Prostate Cancer Index Composite quality of life (EPIC QOL) scores according to the acute toxicity grade (grade 0–1 vs grade 2–3). Grade 0–1 in blue line, grade 2–3 in red line. Changes in the following urinary domains and subscales are shown: (a) general urinary, (b) function, (c) bother, (d) irritation, and (e) incontinence.



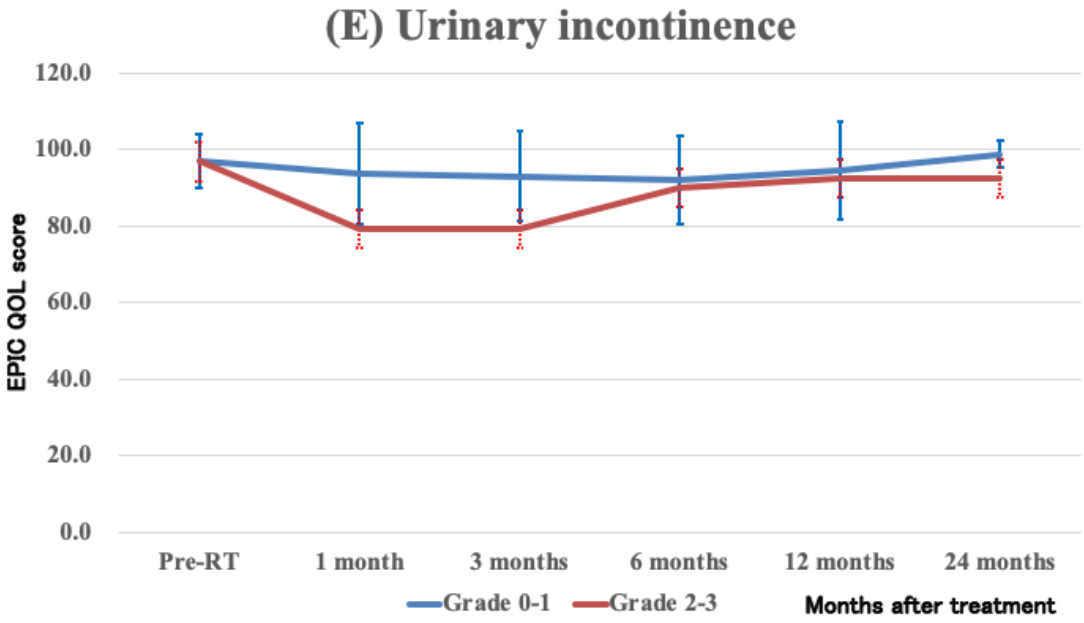
Acute GU						
Grade 0-1	97.2 ± 6.4	87.6 ± 12.4	89.9 ± 12.8	92.0 ± 12.1	96.4 ± 7.7	99.1 ± 2.9
Grade 2-3	98.1 ± 4.2	76.6 ± 17.6	83.1 ± 17.9	90.7 ± 12.7	94.6 ± 11.7	95.7 ± 8.6



Acute GU						
Grade 0-1	97.2 ± 6.4	87.6 ± 12.4	89.9 ± 12.8	92.0 ± 12.1	96.4 ± 7.7	99.1 ± 2.9
Grade 2-3	98.1 ± 4.2	76.6 ± 17.6	83.1 ± 17.9	90.7 ± 12.7	94.6 ± 11.7	95.7 ± 8.6

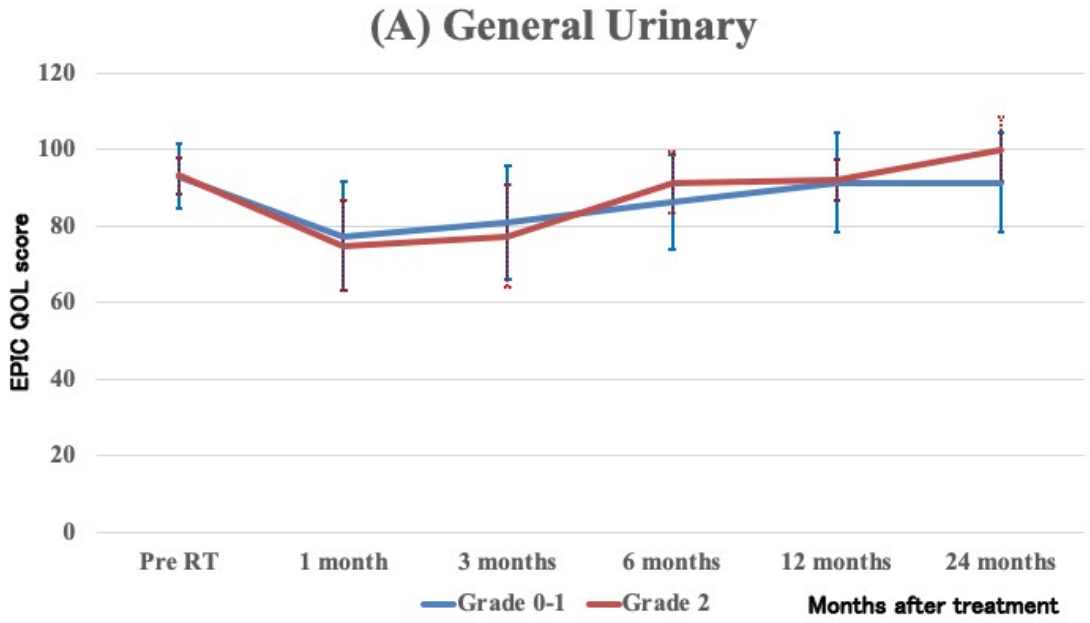


Acute GU						
Grade 0-1	91.7 ± 10.7	76.7 ± 16.0	81.0 ± 14.6	85.7 ± 13.9	92.4 ± 7.2	95.0 ± 6.4
Grade 2-3	93.7 ± 6.0	67.2 ± 16.9	75.8 ± 16.6	85.0 ± 13.6	91.7 ± 11.5	91.6 ± 9.0

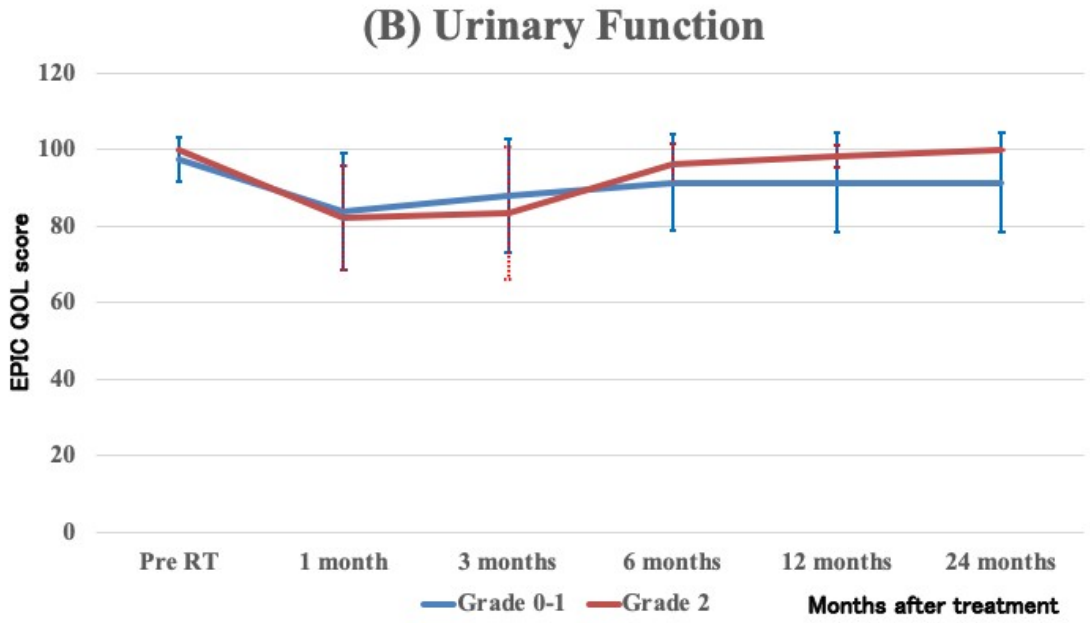


Acute GU						
Grade 0-1	97.1 ± 11.4	93.8 ± 13.2	93.0 ± 11.8	92.1 ± 11.4	94.5 ± 12.7	98.8 ± 3.6
Grade 2-3	90.1 ± 15.3	79.3 ± 23.3	79.3 ± 25.0	90.1 ± 15.3	92.4 ± 17.6	92.4 ± 14.2

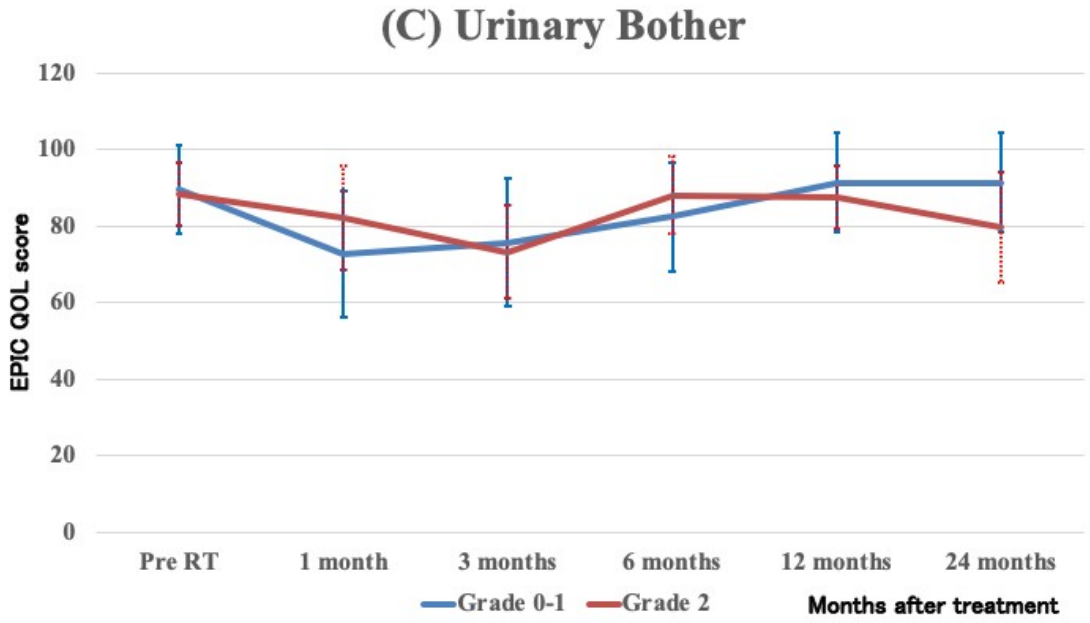
Figure 4. Longitudinal changes in the Expanded Prostate Cancer Index Composite quality of life (EPIC QOL) scores according to the late genitourinary (GU) toxicity grade (grade 0–1 vs grade 2–3). Grade 0–1 in blue line, grade 2–3 in red line. Changes in the following urinary domains and subscales are shown: (a) general urinary, (b) function, (c) bother, (d) irritation,



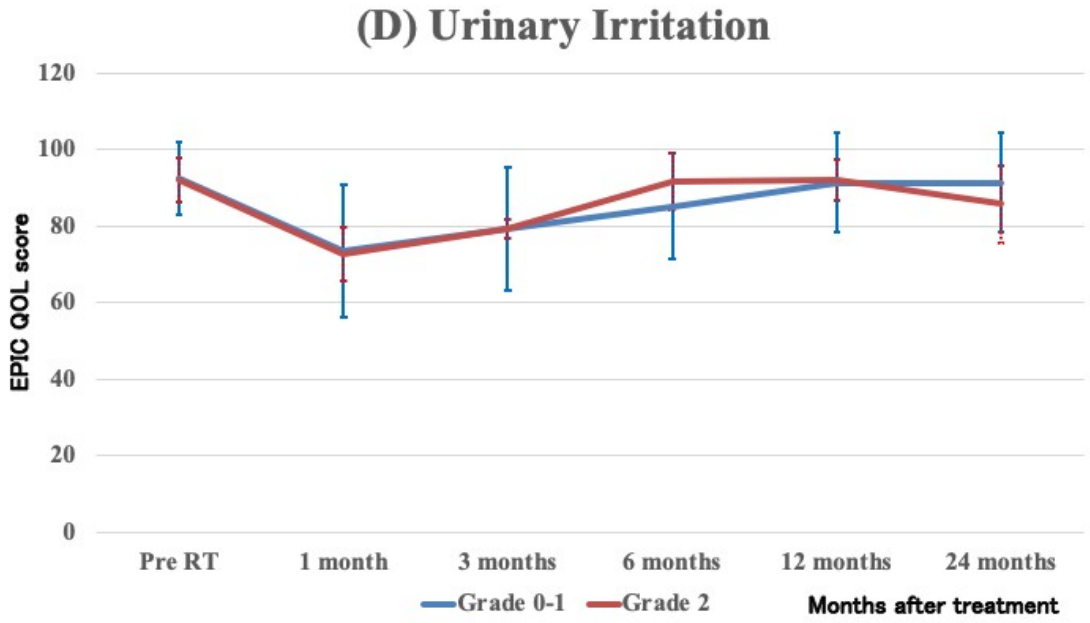
Late GU						
Grade 0-1	93.0 ± 8.3	77.3 ± 14.2	80.8 ± 14.9	86.2 ± 12.4	91.4 ± 12.9	91.4 ± 12.9
Grade 2	93.2 ± 4.7	74.9 ± 11.8	77.4 ± 13.3	91.4 ± 8.1	92.0 ± 5.3	100.o ± 8.4



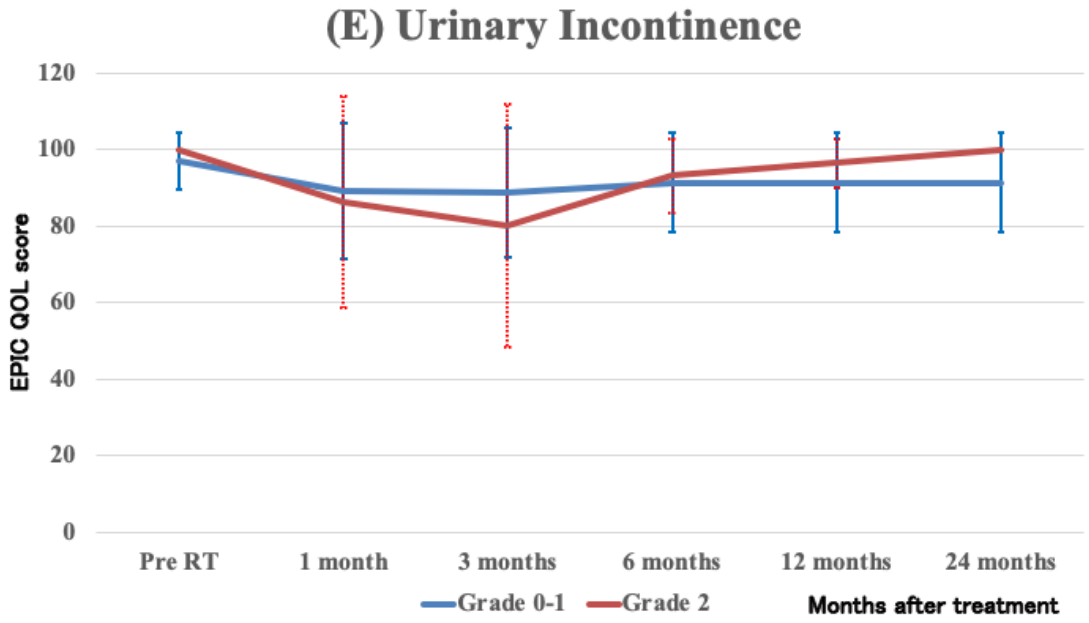
Late GU						
Grade 0-1	97.4 ± 5.8	83.9 ± 15.4	87.9 ± 14.8	91.4 ± 12.4	91.4 ± 12.9	91.4 ± 12.9
Grade 2	100.0 ± 0	82.0 ± 13.6	83.3 ± 17.4	96.1 ± 5.5	98.4 ± 2.9	100.0 ± 0



Late GU						
Grade 0-1	89.7 ± 11.5	72.6 ± 16.4	75.7± 16.6	82.5 ± 14.2	91.4 ± 12.9	91.4 ± 12.9
Grade 2	88.4 ± 8.1	82.1 ± 13.7	73.2 ± 12.2	88.1 ± 10.2	87.5 ± 8.2	79.8 ± 14.4



Late GU						
Grade 0-1	92.4 ± 9.5	73.4 ± 17.3	79.2 ± 16.0	85.2 ± 13.8	91.4 ± 12.9	91.4 ± 12.9
Grade 2	92.0 ± 5.9	72.7 ± 7.1	79.2 ± 2.5	91.7 ± 7.3	92.0 ± 5.3	85.7 ± 10.1



Late GU						
Grade 0-1	96.9 ± 7.3	89.0 ± 17.8	88.9 ± 16.9	91.4 ± 12.9	91.4 ± 12.9	91.4 ± 12.9
Grade 2	100.0 ± 0	86.3 ± 27.5	80.2 ± 31.8	93.1 ± 9.8	96.4 ± 6.3	100.0 ± 0