Quality of life in patients who underwent $^{125}$I brachytherapy, $^{125}$I brachytherapy combined with three-dimensional conformal radiation therapy, or intensity-modulated radiation therapy, for prostate cancer

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(Received 2 September 2018; revised 4 October 2018; editorial decision 18 October 2018)

ABSTRACT
The purpose of this study was to evaluate quality of life (QOL) in prostate cancer patients treated with $^{125}$I brachytherapy (BT), $^{125}$I brachytherapy combined with 3D conformal radiation therapy (BT+3D-CRT), or intensity-modulated radiation therapy (IMRT). We evaluated disease-related QOL in patients who underwent BT, BT+3D-CRT, or IMRT, using the Expanded Prostate Cancer Index Composite questionnaire before treatment and at 3 and 24 months post-treatment. Multivariate analyses were conducted to determine factors associated with a minimum important difference (MID) in urinary, bowel, sexual, and hormone domain scores at 3 and 24 months post-treatment. Of 558 enrolled patients (IMRT, 123; BT, 230; and BT+3D-CRT, 205), urinary domain scores showed a MID after BT, BT+3D-CRT and IMRT at 3 months in 69%, 84% and 25% of patients, respectively, and at 24 months in 43%, 54% and 28% of patients, respectively. On multivariate analysis, BT+3D-CRT (3 months: odds ratio (OR) = 12.7; $P < 0.001$; 24 months: OR = 3.29; $P = 0.001$) and BT (3 months: OR = 6.28; $P < 0.001$ and 24 months: OR = 2.22; $P = 0.027$) were associated with more severely worsened urinary QOL than IMRT. Bowel domain scores showed a MID at 3 months after BT, BT+3D-CRT and IMRT at 3 months in 69%, 84% and 25% of patients, respectively, and at 24 months in 43%, 54% and 28% of patients, respectively. On multivariate analysis, BT+3D-CRT (3 months: OR = 4.20; $P < 0.001$ and 24 months: OR = 2.63; $P < 0.001$) and IMRT (24 months: OR = 1.98; $P = 0.029$) were associated with more severely worsened bowel QOL than was BT. Information about the changes in QOL outcomes associated with radiotherapy modalities could guide treatment decisions.

Keywords: brachytherapy; brachytherapy with three-dimensional conformal radiation therapy; prostate cancer; intensity-modulated radiation therapy; Quality of Life

INTRODUCTION
Currently, we can use several definitive treatment modalities such as $^{125}$I brachytherapy (BT), BT combined with external-beam radiation therapy (EBRT), and intensity-modulated radiation therapy (IMRT) for localized and locally advanced prostate cancer. Each modality has advantages and disadvantages, and exerts a distinct impact on quality of life (QOL), particularly with regard to urinary, bowel, sexual and hormonal health [1–5]. Evans et al. found that...
BT worsened urinary-related QOL, compared with IMRT and stereotactic body radiotherapy (SBRT) [3]. However, the study did not include a BT and EBRT combination therapy group (this option is beneficial in intermediate-risk and high-risk prostate cancer). Amini et al. reported that compared with EBRT alone, combination therapy with BT and EBRT decreased the risk of death in intermediate- and high-risk prostate cancer (75.6–81 Gy) [5]. Recently, the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial showed a progression-free survival benefit of the combination therapy with BT and EBRT (hazard ratio = 0.473; \( P = 0.0022 \)) [6]. These results showed the superiority of combination therapy with BT and EBRT in patients with intermediate-risk and high-risk prostate cancer.

Due to the impact of urinary, rectal, sexual and hormonal side effects of radiation treatment [1–5], QOL changes after each of the radiotherapy options is important to consider. The Expanded Prostate Cancer Index Composite (EPIC) is a validated tool that measures disease-related QOL in four domains relevant to patients with localized prostate cancer [7]. Morton et al. reported that the EPIC was a more sensitive tool for detecting effects on function and bother than were the generic toxicity scales [8, 9]. However, to our knowledge, there are no reports comparing QOL in groups receiving IMRT, BT, or the combination therapy with BT and EBRT. Thus, we aimed to evaluate and compare QOL after BT, after BT combined with 3D conformal radiation therapy (BT + 3D-CRT), and after IMRT, using the EPIC questionnaire.

**MATERIALS AND METHODS**

**Patients**

This study was conducted in accordance with the provisions of the Declaration of Helsinki (59th World Medical Association General Assembly, Seoul, Korea, in October 2008), and the study protocol was approved by the ethics committee. Data on disease-related QOL in patients who underwent BT, BT + 3D-CRT, and IMRT from April 2010 to March 2014 at the Nara Medical University was collected (prospectively). All patients who received radiation therapy during the study period were offered the opportunity to participate in this study. The study aims and methodologies were explained, and the questionnaire and a leaflet about this study were given to each patient. All patients who answered the questionnaire were enrolled in this study.

**Radiation therapy**

The BT group was treated by seed implantation alone at a dose of 160 Gy, whereas the BT + 3D-CRT group was treated at a dose of 110 Gy. The target portion of 3D-CRT was determined 1 month after seed implantation, and patients received a cumulative dose of 45 Gy divided into 25 fractions (1.8 Gy per fraction) using 10 MV photon beams. The clinical target volume included the entire prostate and the proximal third of the seminal vesicles [10]. IMRT was given at a dose of 74–76 Gy in 2-Gy fractions with a 1-cm or 6-mm margin at the prostate–rectum interface. In general, elective lymph node irradiation was not routinely employed during this study period, and patients did not undergo pretreatment fiducial marker placement for image guidance during daily fractions.

**Quality of life**

EPIC questionnaires were given to enrolled patients before treatment (i.e. baseline) and at 1, 3, 6, 12 and 24 months post-treatment. A minimally important difference (MID), or a lack of return to baseline, was defined as a parameter value that was greater than half a standard deviation from its baseline value, in all patients who underwent the particular treatment [1, 11].

**Variables**

The prostate-specific antigen (PSA) value at diagnosis and the prostate volume measured during prostate biopsy were used for analysis. Uroflowmetry was performed within the month preceding each radiation treatment, and the maximum flow rate (Qmax) and the post-void residual (PVR) were used as parameters in this study.

**Statistical analysis**

Statistical analysis was performed using SPSS for Windows (version 20.0; IBM, Armonk, NY, USA). The Mann–Whitney U-test was used for continuous variables, and the chi-square test was used for categorical variables. Multivariate logistic regression analysis was used to identify predictive factors for the occurrence of lowering the scores by a MID or more from baseline scores at 3 and 24 months. Among the BT, BT + 3D-CRT, and IMRT groups, the group with the lowest percentage of patients displaying a MID was chosen as the reference. A \( P \) value of < 0.05 was considered statistically significant, and the Bonferroni correction for multiple comparisons was used where appropriate.

**RESULTS**

**Characteristics of enrolled patients**

The numbers of patients enrolled were 141 for IMRT, 235 for BT, and 213 for BT + 3D-CRT. At baseline, the EPIC questionnaire was completed for 123 patients treated with IMRT, for 230 patients treated with BT, and for 205 patients treated with BT + 3D-CRT. The mean age of the IMRT group was significantly older than that of the BT (\( P < 0.001 \)) and the BT + 3D-CRT (\( P < 0.001 \)) groups; the mean age of the BT + 3D-CRT group (\( P < 0.001 \)) was significantly older than that of the BT group. At diagnosis, compared with the BT group, the BT + 3D-CRT (\( P < 0.001 \)) and the IMRT (\( P < 0.001 \)) groups had higher PSA values; the IMRT group (\( P < 0.001 \)) had a higher PSA value than the BT + 3D-CRT group at diagnosis. The prostate volume of the BT + 3D-CRT group was significantly smaller (\( P < 0.001 \)) than that of the BT group, whereas the prostate volume of the IMRT group was smaller than that of the BT group (\( P = 0.002 \)). The proportion of high-risk patients, by National Comprehensive Cancer Network (NCCN) classification criteria in the IMRT, BT, and BT + 3D-CRT groups was 47.1%, 1.7% and 42.9%, respectively. The proportion of intermediate-risk patients by NCCN classification criteria in the IMRT, BT, and BT + 3D-CRT groups was 43.0%, 52.1% and 55.1%, respectively. The proportion of low-risk patients by NCCN classification criteria in the IMRT, BT, and BT + 3D-CRT groups was 9.8%, 46.1% and 2.0%, respectively.
respectively. The mean maximum flow rate of the IMRT group was significantly lower than that of the BT ($P < 0.001$) and the BT + 3D-CRT ($P < 0.001$) groups. The mean PVR value was significantly higher in the IMRT group than in the BT ($P < 0.001$) and the BT + 3D-CRT ($P < 0.001$) groups (Table 1).

**Urinary domain**

Chronological changes in urinary domain scores are shown in Table 2. The percentage of patients who lowered the score by the MID or more from baseline in the urinary domain at 3 months after BT, BT + 3D-CRT, and IMRT was 69%, 84% and 25%, respectively (Table 3). Multivariate analysis showed that, using the IMRT group as the reference, a greater number of patients in the BT group (OR = 1.98; 95% CI = 1.07–3.67) and the BT + 3D-CRT (OR = 2.63; 95% CI = 1.57–4.42) groups showed a MID from baseline in the bowel domain at 24 months post-treatment (Table 5).

**Bowel domain**

Chronological changes in bowel domain scores are shown in Table 2. The percentage of patients who lowered the score by a MID or more from baseline in the bowel domain at 3 months after BT, BT + 3D-CRT, and IMRT was 37%, 68% and 41%, respectively (Table 3). In multivariate analysis, using the BT group as the reference, a greater number of patients in the BT + 3D-CRT group (OR = 4.20; 95% CI = 2.53–6.98) showed a MID from baseline at 3 months after treatment whereas, there was no significant difference between the IMRT group and the BT group (OR = 1.16; 95% CI = 0.65–2.10) (Table 5). The percentage of patients who lowered the score by a MID or more from baseline in the bowel domain at 24 months after BT, BT + 3D-CRT, and IMRT was 29%, 49% and 43%, respectively (Table 3). Multivariate analysis showed that, using the BT group as a reference, a greater number of patients in the IMRT group (OR = 1.98; 95% CI = 1.07–3.67) and the BT + 3D-CRT (OR = 2.63; 95% CI = 1.57–4.42) groups showed a MID from baseline in the bowel domain at 24 months post-treatment (Table 5).

**Sexual domain**

Chronological changes in the sexual domain score are shown in Table 2. The percentage of patients with a MID from baseline in the sexual domain at 3 months after BT, BT + 3D-CRT, and IMRT were 23%, 17% and 23%, respectively (Table 3). Multivariate analysis showed that at 3 months post-treatment, treatment modality was not a significant factor for MID from baseline in sexual QOL (Table 6). The percentage of patients who lowered the score by a MID or more from baseline in the sexual domain at 24 months after BT, BT + 3D-CRT, and IMRT was 28%, 16% and 28%, respectively (Table 3). Multivariate analysis showed that, using the BT + 3D-CRT groups as a reference, a greater number of patients in the IMRT group (OR = 3.41; 95% CI = 1.71–6.82) showed a MID difference from baseline at 24 months after treatment (Table 6).

**Table 1. Baseline characteristics of patients with prostate cancer who underwent radiation therapy**

|                      | IMRT     | BT      | BT + 3D-CRT |
|----------------------|----------|---------|-------------|
| Median (range) or n  | ($n = 123$) | ($n = 230$) | ($n = 205$) |
| Age, years           | 73 (52–82) | 69 (48–81)** | 70 (49–84)**†† |
| PSA, ng/ml           | 13.1 (3.1–218) | 6.4 (1.2–43.6)** | 9.5 (1.2–113)**†† |
| Prostate volume, ml  | 24.8 (6.9–69.9) | 26.0 (8.7–48.8)* | 20.6 (7.7–52.6)**†† |
| Gleason score, 6:7:8–10 | 15:67:41 | 116:113:1** | 20:126:59†† |
| T stage, T1:T2:T3–4 | 47:37:39 | 131:98:1** | 104:64:37**†† |
| NCCN risk classification, low:intermediate:high | 12:53:58 | 106:120:4** | 4:113:88**†† |
| Qmax, ml/s           | 9.9 (2.9–40.2) | 12.3 (4.1–45.1)** | 11.9 (3.8–35.6)** |
| PVR, ml              | 16.1 (0–147) | 6.8 (0–216)** | 7.8 (0–271)** |
| ADT                  | No:Neo:Neo + adjuvant | 35:16:71 | 140:86:4** | 65:85:54**†† |

* $P < 0.016$; ** $P < 0.001$ vs IMRT; † $P < 0.016$; †† $P < 0.001$ vs BT.

IMRT = intensity-modulated radiation therapy, BT = brachytherapy, 3D-CRT = 3D conformal radiation therapy, PSA = prostate-specific antigen, NCCN = National Comprehensive Cancer Network, Qmax = maximum flow rate, PVR = post-void residual, ADT = androgen-deprivation therapy, Neo = neoadjuvant therapy.
Table 2. Time-course of changes in EPIC questionnaire scores after intensity-modulated radiation therapy (IMRT), brachytherapy (BT), and BT + 3D conformal radiation therapy (3D-CRT) (BT+3D-CRT)

| Domains                  | Baseline scores (Scores (SD)) | Follow-up (months) (Scores (SD)) |
|--------------------------|-------------------------------|----------------------------------|
|                          | 1361                          | 123                              |
|                          | 2                             | 2                                |
|                          | 4                             | 2                                |
| n =                      | IMRT 123                      | BT 230                           |
|                          | BT 205                        | BT + 3D-CRT 205                  |

Urinary summary

| Overall | Overall | IMRT | BT | BT + 3D-CRT |
|---------|---------|------|----|-------------|
| Overall | 95.3 (6.6) | 94.1 (7.4) | 95.9 (5.5) | 95.5 (7.2) |
|         | 85.3 (13.4) | 89.3 (10.5) | 83.2 (13.6) | 85.2 (14.2) |
|         | 85.4 (13.8) | 94.2 (7.4) | 85.5 (13.0) | 80.1 (14.7) |
|         | 89.7 (10.1) | 94.5 (6.5) | 88.4 (11.5) | 88.3 (11.8) |
|         | 92.4 (10.2) | 94.2 (8.1) | 92.5 (10.1) | 91.3 (11.2) |
|         | 89.7 (12.3) | 92.8 (10.0) | 90.4 (11.5) | 87.0 (13.8) |

(1) Urinary function

| Overall | Overall | IMRT | BT | BT + 3D-CRT |
|---------|---------|------|----|-------------|
| Overall | 96.0 (8.4) | 94.0 (10.0) | 96.5 (7.4) | 96.5 (8.2) |
|         | 85.1 (16.3) | 89.2 (13.3) | 82.6 (16.6) | 85.3 (17.1) |
|         | 86.2 (15.7) | 94.6 (9.6) | 86.7 (15.3) | 80.8 (16.7) |
|         | 89.9 (13.4) | 94.4 (9.3) | 88.7 (13.5) | 88.6 (14.7) |
|         | 92.4 (12.6) | 94.5 (10.3) | 92.3 (12.1) | 90.9 (14.0) |
|         | 88.6 (16.0) | 92.2 (13.8) | 89.5 (14.7) | 85.5 (18.1) |

(2) Urinary bother

| Overall | Overall | IMRT | BT | BT + 3D-CRT |
|---------|---------|------|----|-------------|
| Overall | 95.1 (7.2) | 94.1 (8.1) | 95.4 (6.6) | 94.7 (7.9) |
|         | 84.3 (14.6) | 89.4 (13.3) | 83.6 (14.3) | 85.1 (14.7) |
|         | 82.2 (15.5) | 93.9 (9.6) | 84.6 (14.3) | 79.5 (16.3) |
|         | 88.1 (12.2) | 94.6 (6.8) | 88.1 (12.4) | 88.0 (11.9) |
|         | 92.0 (10.9) | 94.0 (8.0) | 92.4 (11.8) | 91.7 (11.1) |
|         | 90.3 (11.9) | 93.2 (8.8) | 90.9 (11.3) | 88.0 (13.5) |

(3) Urinary irritation

| Overall | Overall | IMRT | BT | BT + 3D-CRT |
|---------|---------|------|----|-------------|
| Overall | 97.3 (5.1) | 95.8 (7.5) | 97.5 (4.8) | 97.0 (5.4) |
|         | 84.4 (15.4) | 91.7 (9.8) | 82.7 (15.8) | 86.4 (14.8) |
|         | 84.8 (14.6) | 96.3 (5.7) | 87.1 (13.5) | 82.2 (15.3) |
|         | 91.0 (11.1) | 96.6 (6.1) | 87.1 (13.5) | 91.4 (10.2) |
|         | 93.5 (10.6) | 95.8 (7.7) | 94.0 (9.9) | 93.1 (11.2) |
|         | 92.1 (11.7) | 95.8 (7.3) | 92.5 (11.2) | 89.4 (13.2) |

(4) Urinary incontinence

| Overall | Overall | IMRT | BT | BT + 3D-CRT |
|---------|---------|------|----|-------------|
| Overall | 96.0 (9.9) | 94.5 (10.9) | 96.1 (8.7) | 95.8 (11.0) |
|         | 89.0 (16.4) | 90.0 (15.8) | 89.0 (15.6) | 89.0 (17.3) |
|         | 85.7 (18.5) | 94.1 (12.1) | 88.2 (17.6) | 83.1 (19.1) |
|         | 88.8 (17.1) | 94.4 (10.9) | 89.1 (16.2) | 88.5 (18.1) |
|         | 92.9 (14.7) | 94.6 (12.0) | 93.6 (13.7) | 92.1 (15.6) |
|         | 89.2 (17.7) | 90.1 (16.1) | 90.3 (16.3) | 87.0 (19.8) |

Bowel summary

Continued
Hormone domain

Chronological changes in hormone domain scores are shown in Table 2. The percentage of patients who lowered the score by a MID or more from baseline in the hormonal domain at 3 months after BT, BT + 3D-CRT, and IMRT was 22%, 24% and 34%, respectively (Table 3). The percentage of patients who lowered the score by a MID or more from baseline in the sexual domain at 24 months after BT, BT + 3D-CRT, and IMRT was 14%, 23% and 32%, respectively (Table 3). Multivariate analysis showed that at 3 months and at 24 months post-treatment, treatment modality was not a significant factor for hormone domain QOL changes (Table 7).

DISCUSSION

To the best of our knowledge, ours is the first study to comparatively evaluate the effect of BT, BT + 3D-CRT, and IMRT on

Table 2. Continued

| Domains          | Baseline scores (SD) | Follow-up (months) | 1 (SD) | 3 (SD) | 6 (SD) | 12 (SD) | 24 (SD) |
|------------------|----------------------|--------------------|-------|-------|-------|--------|--------|
| Overall          | 95.3 (6.2)           | 92.4 (8.4)         | 90.9 (9.8) | 92.8 (8.0) | 93.0 (8.1) | 92.6 (9.2) |
| IMRT             | 95.1 (7.1)           | 91.0 (9.2)         | 93.4 (12.1) | 95.0 (5.8) | 91.6 (9.3) | 90.4 (13.0) |
| BT               | 95.5 (5.6)           | 92.8 (8.3)         | 93.0 (8.1) | 93.1 (8.0) | 94.5 (6.3) | 94.9 (6.6) |
| BT + 3D-CRT      | 95.1 (6.3)           | 92.8 (8.0)         | 87.1 (11.7) | 91.4 (8.8) | 92.2 (8.8) | 91.6 (8.9) |

(1) Bowel function

| Domains          | Baseline scores (SD) | Follow-up (months) | 1 (SD) | 3 (SD) | 6 (SD) | 12 (SD) | 24 (SD) |
|------------------|----------------------|--------------------|-------|-------|-------|--------|--------|
| Overall          | 93.9 (8.7)           | 88.8 (11.4)        | 86.9 (12.4) | 89.5 (10.9) | 89.7 (11.0) | 89.4 (11.7) |
| IMRT             | 97.4 (7.3)           | 87.0 (12.0)        | 90.0 (9.7) | 92.4 (8.8) | 87.9 (12.3) | 87.7 (14.6) |
| BT               | 93.3 (8.3)           | 89.3 (11.1)        | 89.5 (11.1) | 89.8 (10.6) | 91.4 (9.3) | 92.0 (9.3) |
| BT + 3D-CRT      | 92.5 (9.3)           | 89.2 (11.3)        | 82.2 (13.6) | 87.5 (11.8) | 88.7 (11.7) | 87.7 (11.8) |

(2) Bowel bother

| Domains          | Baseline scores (SD) | Follow-up (months) | 1 (SD) | 3 (SD) | 6 (SD) | 12 (SD) | 24 (SD) |
|------------------|----------------------|--------------------|-------|-------|-------|--------|--------|
| Overall          | 97.7 (5.1)           | 96.0 (7.1)         | 94.9 (8.9) | 96.2 (6.7) | 96.4 (6.6) | 95.8 (8.6) |
| IMRT             | 97.4 (7.3)           | 94.5 (7.9)         | 96.8 (5.3) | 97.5 (3.8) | 95.3 (7.8) | 93.1 (12.7) |
| BT               | 97.8 (4.3)           | 96.2 (7.2)         | 96.3 (7.0) | 96.5 (6.6) | 97.6 (4.6) | 97.6 (5.2) |
| BT + 3D-CRT      | 97.9 (4.2)           | 96.4 (6.3)         | 92.0 (11.6) | 95.3 (8.4) | 95.3 (8.7) | 95.4 (8.1) |

Sexual summary

| Domains          | Baseline scores (SD) | Follow-up (months) | 1 (SD) | 3 (SD) | 6 (SD) | 12 (SD) | 24 (SD) |
|------------------|----------------------|--------------------|-------|-------|-------|--------|--------|
| Overall          | 38.5 (13.0)          | 35.5 (10.4)        | 35.8 (11.4) | 36.1 (10.9) | 36.4 (11.5) | 36.2 (12.1) |
| IMRT             | 38.2 (11.5)          | 33.9 (9.6)         | 33.8 (9.6) | 33.5 (8.7) | 33.5 (8.4) | 32.5 (10.3) |
| BT               | 40.8 (14.2)          | 36.9 (10.4)        | 37.8 (12.5) | 38.0 (12.0) | 38.6 (12.8) | 38.6 (13.5) |
| BT + 3D-CRT      | 36.2 (12.1)          | 35.0 (10.6)        | 34.7 (10.8) | 35.5 (10.6) | 35.6 (11.1) | 35.7 (10.9) |

Hormone summary

| Domains          | Baseline scores (SD) | Follow-up (months) | 1 (SD) | 3 (SD) | 6 (SD) | 12 (SD) | 24 (SD) |
|------------------|----------------------|--------------------|-------|-------|-------|--------|--------|
| Overall          | 92.9 (8.6)           | 92.8 (8.7)         | 93.3 (8.1) | 94.2 (7.8) | 94.2 (7.8) | 94.4 (8.0) |
| IMRT             | 95.1 (7.1)           | 92.1 (8.4)         | 92.8 (7.8) | 93.1 (8.2) | 93.3 (7.0) | 92.0 (9.3) |
| BT               | 93.1 (8.3)           | 94.5 (7.5)         | 94.7 (7.1) | 95.2 (6.6) | 95.9 (5.5) | 96.4 (5.0) |
| BT + 3D-CRT      | 91.2 (9.3)           | 91.4 (9.6)         | 91.9 (9.1) | 93.7 (8.7) | 92.9 (9.4) | 93.4 (9.3) |

EPIC = Expanded Prostate Cancer Index Composite, IMRT = intensity-modulated radiation therapy, BT = brachytherapy, 3D-CRT = 3D conformal radiation therapy, IPSS = International Prostate Symptom Score, QOL = quality of life, SD = standard deviation.
Table 3. Percentage of patients who showed a decrease (minimally important difference) in quality-of-life scores from own baseline scores

| Domains       | Follow-up (months) | % (n)     | 1 | 3 | 6 | 12 | 24 |
|---------------|--------------------|-----------|---|---|---|----|----|
|               |                    |           |   |   |   |    |    |
| Urinary summary | IMRT               | 36 (44/123) | 25 (31/123) | 24 (29/121) | 26 (31/121) | 28 (34/121) |
|                | BT                 | 73 (165/227) | 69 (156/227) | 60 (136/227) | 35 (79/227) | 43 (95/221) |
|                | BT + 3D-CRT        | 64 (131/205) | 84 (173/205) | 58 (118/205) | 40 (83/205) | 54 (114/201) |
| Bowel summary  | IMRT               | 52 (64/123) | 41 (50/123) | 33 (40/121) | 45 (54/121) | 43 (52/121) |
|                | BT                 | 40 (91/227) | 37 (84/227) | 37 (85/227) | 31 (70/227) | 29 (64/221) |
|                | BT + 3D-CRT        | 39 (80/205) | 68 (139/205) | 46 (95/205) | 41 (84/205) | 46 (92/201) |
| Sexual summary | IMRT               | 31 (22/123) | 23 (28/123) | 25 (30/121) | 21 (25/121) | 28 (34/121) |
|                | BT                 | 27 (62/227) | 23 (52/227) | 26 (58/227) | 26 (58/227) | 28 (62/221) |
|                | BT + 3D-CRT        | 15 (30/205) | 17 (34/205) | 15 (30/205) | 18 (36/205) | 16 (33/201) |
| Hormone summary | IMRT               | 40 (49/123) | 34 (42/123) | 32 (39/121) | 36 (44/121) | 32 (39/121) |
|                | BT                 | 21 (40/227) | 22 (49/227) | 18 (40/227) | 15 (35/227) | 14 (31/221) |
|                | BT + 3D-CRT        | 25 (51/205) | 24 (49/205) | 19 (39/205) | 22 (46/205) | 23 (47/201) |

EPIC = Expanded Prostate Cancer Index Composite, IMRT = intensity-modulated radiation therapy, IPSS = International Prostate Symptom Score, QOL = quality of life, BT = brachytherapy, 3D-CRT = 3D conformal radiation therapy, SD = standard deviation.

Table 4. Uni- and multivariate analysis of factors to predict a decrease (minimally important difference) in urinary domain scores from own baseline score at 3 and 24 months

| Variables                  | 3 months after radiation therapy | 24 months after radiation therapy | Analysis |
|----------------------------|----------------------------------|----------------------------------|----------|
|                            | Univariate                        | Multivariate                     | Univariate| Multivariate|          |
|                            | P OR (95% CI)                     | P OR (95% CI)                    | P OR (95% CI) | P OR (95% CI) | P |
| Age                        | 0.31 0.98 (0.94–1.02)             | 0.22 0.97 (0.94–1.01)            | 0.15 1.10 (0.99–1.03) | 0.077 0.44 |
| Prostate volume            | 0.04 1.02 (0.99–1.05)             | 0.09 1.09 (0.99–1.03)            | 0.43 1.10 (0.99–1.03) | 0.44 |
| NCCN risk classification   | Low Ref Ref                        | Ref Ref                          | Ref Ref | Ref Ref | Ref Ref |
| Intermediate               | 0.48 1.31 (0.74–2.33)             | 0.36 1.60 (0.93–2.76)            | 0.08 1.60 (0.93–2.76) | 0.09 |
| High                       | 0.88 0.93 (0.36–2.42)             | 0.88 1.11 (0.49–2.53)            | 0.22 1.11 (0.49–2.53) | 0.81 |
Table 4. Continued

| Variables          | Analysis                  | 3 months after radiation therapy | 24 months after radiation therapy |
|--------------------|---------------------------|----------------------------------|-----------------------------------|
|                    | Univariate                | Multivariate                     | Univariate                       | Multivariate                     |
|                    | P                         | OR (95% CI)                      | P                                 | OR (95% CI)                      |
| Qmax               | 0.78                      | 0.98 (0.94–1.01)                 | 0.23                              | 0.85                             | 0.98 (0.95–1.02)                 | 0.3 |
| PVR                | 0.02                      | 1.00 (0.99–1.01)                 | 0.56                              | 0.18                             | 1.00 (0.99–1.01)                 | 0.4 |
| ADT                |                           |                                  |                                   |                                  |
| No                 | Ref                       | Ref                              | Ref                              | Ref                              |
| Neo                | <0.01                     | 2.40 (1.38–4.2)                  | 0.002                            | 0.04                             | 1.27 (0.80–2.01)                 | 0.32 |
| Neo+adjuvant       | 0.51                      | 2.59 (1.04–6.48)                 | 0.041                            | 0.49                             | 1.75 (0.82–3.72)                 | 0.15 |
| Radiation therapy  |                           |                                  |                                   |                                  |
| IMRT               | Ref                       | Ref                              | Ref                              | Ref                              |
| BT                 | <0.01                     | 6.28 (2.94–13.4)                 | <0.001                           | 2.22 (1.10–4.53)                 | 0.027 |
| BT + 3D-CRT        | <0.01                     | 12.7 (6.02–26.9)                 | <0.001                           | 3.29 (1.67–6.45)                 | 0.001 |
| Baseline domain    | 0.04                      | 1.04 (1.01–1.08)                 | 0.033                            | 0.73                             | 0.97 (0.94–1.01)                 | 0.099 |

IMRT = intensity-modulated radiation therapy, BT = brachytherapy, 3D-CRT = 3D conformal radiation therapy, Qmax = maximum flow rate, PVR = post-void residual, ADT = androgen-deprivation therapy, Neo = neoadjuvant therapy, NCCN = National Comprehensive Cancer Network, CI = confidence interval, OR = odds ratio.

Table 5. Uni- and multivariate analysis of factors to predict occurrence of a decrease (minimally important difference) in bowel domain from own baseline score at 3 and 24 months post-treatment

| Variables          | Analysis                  | 3 months after radiation therapy | 24 months after radiation therapy |
|--------------------|---------------------------|----------------------------------|-----------------------------------|
|                    | Univariate                | Multivariate                     | Univariate                       | Multivariate                     |
|                    | P                         | OR (95% CI)                      | P                                 | OR (95% CI)                      |
| Age                | 0.88                      | 0.99 (0.97–1.03)                 | 0.94                              | 0.01                             | 1.05 (1.01–1.08)                 | 0.006 |
| Prostate volume    | 0.17                      | 1.01 (0.99–1.03)                 | 0.49                              | 0.42                             | 1.02 (0.99–1.04)                 | 0.08  |
| NCCN risk classification |                       |                                  |                                   |                                  |
| Low                | Ref                       | Ref                              | Ref                              | Ref                              |
| Intermediate       | 0.04                      | 0.99 (0.97–1.03)                 | 0.99                              | 0.68                             | 0.78 (0.45–1.35)                 | 0.38  |
| High               | <0.01                     | 1.21 (0.56–2.63)                 | 0.62                              | 0.07                             | 0.86 (0.39–1.86)                 | 0.69  |
| ADT                |                           |                                  |                                   |                                  |
| No                 | Ref                       | Ref                              | Ref                              | Ref                              |
| Neo                | 0.66                      | 0.76 (0.49–1.18)                 | 0.22                              | 0.04                             | 1.10 (0.75–1.63)                 | 0.63  |
| Neo+adjuvant       | 0.35                      | 0.69 (0.35–1.38)                 | 0.29                              | 0.49                             | 1.21 (0.77–1.92)                 | 0.41  |

Radiation therapy

Continued
Table 5. Continued

| Variables          | Analysis | 3 months after radiation therapy | 24 months after radiation therapy | Analysis | 3 months after radiation therapy | 24 months after radiation therapy |
|--------------------|----------|----------------------------------|----------------------------------|----------|----------------------------------|----------------------------------|
|                    |          | Univariate | Multivariate | OR (95% CI) | P | Univariate | Multivariate | OR (95% CI) | P |
| BT                 | Ref      | Ref        | Ref          | Ref         |   | 0.38        | 1.16 (0.65–2.10) | 0.61         | <0.01    | 1.98 (1.07–3.67) | 0.029 |
| IMRT               |          |            |              |             |   | BT + 3D-CRT | 4.20 (2.53–6.98) | <0.001       | 2.63 (1.57–4.42) | <0.001 |
| Baseline domain    | <0.01    |            |              |             |   | <0.01       | 1.08 (1.04–1.12) | <0.001       | 1.08 (1.04–1.12) | <0.001 |

IMRT = intensity-modulated radiation therapy, BT = brachytherapy, 3D-CRT = 3D conformal radiation therapy, NCCN = National Comprehensive Cancer Network, Qmax = maximum flow rate, PVR = post-void residual, ADT = androgen-deprivation therapy, Neo = neoadjuvant therapy, CI = confidence interval, OR = odds ratio.

Table 6. Uni- and multivariate analysis of factors to predict occurrence of a decrease (minimally important difference) in sexual domain scores from own baseline scores at 3 and 24 months post-treatment

| Variables          | Analysis | 3 months after radiation therapy | 24 months after radiation therapy | Analysis | 3 months after radiation therapy | 24 months after radiation therapy |
|--------------------|----------|----------------------------------|----------------------------------|----------|----------------------------------|----------------------------------|
|                    |          | Univariate | Multivariate | OR (95% CI) | P | Univariate | Multivariate | OR (95% CI) | P |
| Age                | <0.01    | 1.00 (0.96–1.05) | 0.93 | 0.01 | 1.06 (1.01–1.11) | 0.025 |
| Prostate volume    | <0.01    | 1.03 (1.01–1.06) | 0.009 | 0.42 | 1.03 (1.002–1.05) | 0.037 |
| NCCN risk classification |          | Ref        | Ref          | Ref         |   | Ref          | Ref          | Ref         |   |
| Low                |          |            |              |             |   | Intermediate | 1.74 (0.88–3.46) | 0.11 | 0.68 | 0.92 (0.47–1.78) | 0.8 |
| High               | <0.01    | 1.34 (0.45–3.99) | 0.6 | 0.07 | 0.90 (0.31–2.63) | 0.84 |
| ADT                |          | Ref        | Ref          | Ref         |   | Ref          | Ref          | Ref         |   |
| No                 |          |            |              |             |   | Neo          | 1.23 (0.61–2.46) | 0.56 | 0.04 | 0.55 (0.28–1.08) | 0.08 |
| Neo+adjuvant       | 0.17     | 2.49 (0.94–6.59) | 0.07 | 0.49 | 1.30 (0.49–3.42) | 0.6 |
| Radiation therapy  |          | Ref        | Ref          | Ref         |   | Ref          | Ref          | Ref         |   |
| BT + 3D-CRT        |          |            |              |             |   | IMRT         | 0.92 (0.43–1.98) | 0.84 | <0.01 | 3.41 (1.71–6.82) | <0.001 |
| BT                 | 0.12     | 1.15 (0.59–2.24) | 0.69 | <0.01 | 1.26 (0.63–2.49) | 0.51 |
| Baseline domain    | <0.01    | 1.10 (1.07–1.12) | <0.001 | <0.01    | 1.11 (1.08–1.14) | <0.001 |

IMRT = intensity-modulated radiation therapy, BT = brachytherapy, 3D-CRT = 3D conformal radiation therapy, NCCN = National Comprehensive Cancer Network, Qmax = maximum flow rate, PVR = post-void residual, ADT = androgen-deprivation therapy, Neo = neoadjuvant therapy, CI = confidence interval, OR = odds ratio.

Evans et al. found that BT caused worse urinary irritation at 2 years ($P < 0.0001$) than did IMRT [3]. The ASCENDE-RT trial showed that a low-dose-rate prostate brachytherapy boost lowered urinary function to a greater extent than did a dose-escalated external beam boost ($−3.6$ vs $−0.5$; $P = 0.04$) [12]. In agreement with the above, in the present study, at 3 and 24 months
after treatment, BT + 3D-CRT was found to lower urinary QOL scores most severely, followed by BT.

In the bowel domain, compared with the BT group, significantly lower QOL scores were seen in the BT + 3D-CRT (3 and 24 months post-treatment), and IMRT groups (24 months post-treatment), on multivariate analysis. Evans et al. reported there was no significant difference in bowel-related QOL between IMRT and BT [3], but Ferrer et al., in agreement with our results, reported that EBRT led to significantly worse bowel summary scores than did BT \( (P < 0.001) \) [13]. The discrepancy in results may be accounted for by the relatively lower QOL scores reported by Evans et al. after BT compared with in the other studies [13, 14], including the present study. The ASCENDE-RT trial showed that there was no significant difference in bowel-related QOL between low-dose-rate prostate brachytherapy boost and a dose-escalated external beam boost [12]. In the present study, the difference between IMRT and BT + 3D-CRT was not evaluated statistically in the bowel domain. However, in agreement with the ASCENDE-RT trial results, the percentages of the patients with a MID in the IMRT and BT + 3D-CRT groups were similar between IMRT (43%) and BT+3D-CRT (46%) at 24 months. Considering the above evidence and the present results, out of BT, BT + 3D-CRT, and IMRT, BT + 3D-CRT may lower bowel QOL most severely, followed by IMRT.

In the sexual domain, IMRT lowered QOL more severely at 24 months post-treatment, compared with BT + 3D-CRT. Although Evans et al. reported no significant differences between the IMRT and BT groups [3], Spratt et al. found that sexual QOL scores were similar between the IMRT and BT + IMRT groups (57.8% vs 55.0%; \( P = 0.67 \) ) [15]. The ASCENDE-RT trial reported lower sexual QOL scores due to a low-dose-rate prostate brachytherapy boost (>22.1 points) than due to a dose-escalated external beam boost (<15.3 points) at 24 months [12]. Although the discrepancy between the above and the present results is difficult to explain, there are a number of possible reasons. The baseline score for the sexual domain in the present study was lower compared with in the other studies, and the patients in the present study were older than those in the other studies [3, 12, 15]. Age and the sexual QOL at baseline are important factors affecting sexual QOL after radiation therapy [4], like the present results (Table 6). Therefore, the differences between the populations may have caused the discrepancy.

### Table 7. Uni- and multivariate analysis of factors to predict occurrence of a decrease (minimally important difference) in hormone domain scores from own baseline scores at 3 and 24 months post-treatment

| Variables                      | 3 months after radiation therapy | 24 months after radiation therapy |
|--------------------------------|----------------------------------|----------------------------------|
|                                | Univariate                       | Multivariate                     | Univariate                       | Multivariate                     |
|                                | \( OR (95\% CI) \)                | \( P \)                           | \( OR (95\% CI) \)                | \( P \)                           |
| Age                            | 0.4                               | 0.99 (0.96–1.03)                  | 0.78                             | 1.02 (0.98–1.06)                  | 0.3                              |
| Prostate volume                | 0.13                              | 1.02 (1.00–1.04)                  | 0.049                            | 1.01 (0.98–1.03)                  | 0.74                             |
| NCCN risk classification       |                                   |                                   |                                   |                                   |                                  |
| Low                            | Ref                               | Ref                               | Ref                               | Ref                               |                                  |
| Intermediate                   | 0.29                              | 1.25 (0.68–2.29)                  | 0.48                             | 1.69 (0.81–3.54)                  | 0.16                             |
| High                           | 0.04                              | 1.17 (0.49–2.79)                  | 0.73                             | <0.01                            | 3.07 (1.14–8.28)                  | 0.027                            |
| ADT                            |                                   |                                   |                                   |                                   |                                  |
| No                             | Ref                               | Ref                               | Ref                               | Ref                               |                                  |
| Neo                            | 0.19                              | 1.95 (1.17–3.31)                  | 0.011                            | 0.58 (0.31–1.07)                  | 0.08                             |
| Neo+adjuvant                   | <0.01                             | 2.86 (1.35–6.05)                  | 0.006                            | 0.89 (0.40–1.98)                  | 0.78                             |
| Radiation therapy              |                                   |                                   |                                   |                                   |                                  |
| BT                             | Ref                               | Ref                               | Ref                               | Ref                               |                                  |
| IMRT                           | 0.04                              | 0.94 (0.48–1.86)                  | 0.87                             | <0.01                            | 1.34 (0.65–2.76)                  | 0.43                             |
| BT + 3D-CRT                    | 0.5                               | 1.07 (0.61–1.89)                  | 0.82                             | <0.01                            | 1.53 (0.82–2.85)                  | 0.18                             |
| Baseline domain                | 0.04                              | 1.07 (1.03–1.10)                  | <0.001                           | <0.01                            | 1.08 (1.04–1.13)                  | <0.001                           |

IMRT = intensity-modulated radiation therapy, BT = brachytherapy, 3D-CRT = 3D conformal radiation therapy, NCCN = National Comprehensive Cancer Network, Qmax = maximum flow rate, PVR = post-void residual, ADT = androgen-deprivation therapy, Neo = neoadjuvant therapy, CI = confidence interval, OR = odds ratio.
In the hormone domain, radiation treatment did not predict a lower EPIC score in the present study at 3 months or 24 months post-treatment. Evans et al. reported that there were no significant differences in hormone-related QOL between seed and IMRT [3], although they did not include androgen-deprivation therapy (ADT) as a factor in the multivariate analysis, which may have affected the results.

BT + 3D-CRT is known to lead to a better prognosis in intermediate- and high-risk prostate cancer [5, 6]; however, QOL in the urinary and bowel domains was higher with BT + 3D-CRT, especially at 3 months post-treatment. Therefore, knowledge of changes in QOL outcomes due to IMRT, BT, and BT + 3D-CRT may guide treatment recommendations and enable patients to make better-informed decisions. Furthermore, patients who undergo BT + 3D-CRT should be offered some treatments for lowered QOL in the 3 months following treatment, to address lower urinary tract symptoms (LUTSs) and bowel function. However, there are few studies on treatments for LUTS and bowel function problems caused by radiation therapy. Calcium-channel blockers and statins for acute rectal toxicity [16], and an alpha-1 blocker or anticholinergic drug for LUTS should be evaluated for improving QOL in future studies [10, 17].

The present study had some limitations. The first limitation was the lack of randomization for type of treatment, which may have led to the possibility that unmeasured selection factors may have influenced the outcomes. Second, the follow-up period was short, considering that the 10-year overall survival rate of patients treated with radiation therapy is relatively high (>70%) [18, 19]. The third limitation was the use of 3D-CRT as a boost after BT. Forsythe et al. reported that BT + 3D-CRT lowered urinary QOL more severely than did BT + IMRT (P < 0.001) [20]. In future studies, a longer follow-up period and inclusion of a BT + IMRT group is indicated.

CONCLUSIONS
Out of BT, BT + 3D-CRT, and IMRT, BT + 3D-CRT lowered urinary and bowel QOL most severely. BT lowered urinary QOL more severely compared with IMRT, and IMRT lowered bowel QOL more severely compared with BT. Knowledge of changes in QOL outcomes associated with IMRT, BT, and BT + 3D-CRT could influence treatment recommendations and enable patients to make better-informed decisions.

CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

FUNDING
None.

REFERENCES
1. Sanda MG, Dunn RL, Michalski J et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008;358:1250–61.
2. Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. J Clin Oncol 2009;27:3916–22.
3. Evans JR, Zhao S, Daignault S et al. Patient-reported quality of life after stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and brachytherapy. Radiother Oncol 2015;116:179–84.
4. Tanaka N, Fujimoto K, Asakawa I et al. Variations in health-related quality of life in Japanese men who underwent iodine-125 permanent brachytherapy for localized prostate cancer. Brachytherapy 2010;9:300–6.
5. Amini A, Jones B, Jackson MW et al. Survival outcomes of dose-escalated external beam radiotherapy versus combined brachytherapy for intermediate- and high-risk prostate cancer using the national cancer data base. J Urol 2016;195:1453–8.
6. Morris WJ, Tyldesley S, Pai HH et al. ASCENDE-RT*: a multicenter, randomized trial of dose-escalated external beam radiotherapy (EBRT-B) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer. J Clin Oncol 2015;33:3.
7. Wei JT, Dunn RL, Litwin MS et al. Development and validation of the Expanded Prostate Cancer Index Composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology 2000;56:899–905.
8. Morton GC, Loblaw DA, Sankreache R et al. Single-fraction high-dose-rate brachytherapy and hypofractionated external beam radiotherapy for men with intermediate-risk prostate cancer: analysis of short- and medium-term toxicity and quality of life. Int J Radiat Oncol Biol Phys 2010;77:811–7.
9. Morton GC, Loblaw DA, Chung H et al. Health-related quality of life after single-fraction high-dose-rate brachytherapy and hypofractionated external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2011;80:1299–305.
10. Tanaka N, Torimoto K, Asakawa I et al. Use of alpha-1 adrenoceptor antagonists in patients who underwent low-dose-rate brachytherapy for prostate cancer—a randomized controlled trial of silodosin versus naftnopilid. Radiat Oncol 2014; 9:302.
11. Parker WR, Wang R, He C et al. Five year expanded prostate cancer index composite-based quality of life outcomes after prostatectomy for localized prostate cancer. BJU Int 2011;107:585–90.
12. Rodda S, Morris WJ, Hamm J et al. ASCENDE-RT*: an analysis of health-related quality of life for a randomized trial comparing low-dose-rate brachytherapy boost with dose-escalated external beam boost for high-and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:581–9.
13. Ferrer M, Suárez JF, Guedea F et al. 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 2008;72:421–32.
14. Hashine K, Kusuhara Y, Miura N et al. Health-related quality of life using SF-8 and EPIC questionnaires after treatment with radical retropubic prostatectomy and permanent prostate brachytherapy. Jpn J Clin Oncol 2009;39:502–8.
15. Spratt DE, Zumsteg ZS, Ghadjar P et al. Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. BJU Int 2014;114:360–7.
16. Zelefsky MJ, Shasha D, Branco RD et al. Prophylactic sildenafil citrate improves select aspects of sexual function in men treated with radiotherapy for prostate cancer. *J Urol* 2014; 192:868–74.

17. Oyama N, Aoki Y, Ito H et al. Alpha 1-adrenoceptor blocker may improve not only voiding but also storage lower urinary tract symptoms caused by $^{125}$I brachytherapy for prostate cancer. *ISRN Urol* 2014;2014:140654.

18. Dearnaley DP, Jovic G, Syndikus I et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014;15:464–73.

19. Bittner N, Merrick GS, Galbreath RW et al. Treatment outcomes with permanent brachytherapy in high-risk prostate cancer patients stratified into prognostic categories. *Brachytherapy* 2015;14:766–72.

20. Forsythe K, Blacksburg S, Stone N et al. Intensity-modulated radiotherapy causes fewer side effects than three-dimensional conformal radiotherapy when used in combination with brachytherapy for the treatment of prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;83:630–5.