Original Article

Correlation between the changes in the EPIC QOL scores and the dose–volume histogram parameters in high-dose-rate brachytherapy combined with hypofractionated external beam radiation therapy for prostate cancer

Yaichiro Hashimoto1, Tetsuo Akimoto1,2,*, Jumpei Iizuka3, Kazunari Tanabe3, and Norio Mitsuhashi1,4

1Department of Radiation Oncology, Tokyo Women’s Medical University, Tokyo, 2Division of Radiation Oncology and Particle Therapy, National Cancer Center Hospital East, Chiba, 3Department of Urology, Tokyo Women’s Medical University, Tokyo, and 4Radiation Therapy Center, Cancer Board Division, Hitachinaka General Hospital, Ibaraki, Japan

*For reprints and all correspondence: Tetsuo Akimoto, Division of Radiation Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: takimoto@east.ncc.go.jp

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Abstract

Objective: To evaluate the correlations between the changes in the quality-of-life scores and the dose–volume histogram parameters in patients receiving high-dose-rate brachytherapy combined with hypofractionated external beam radiation therapy for localized prostate cancer.

Methods: Among the patients who were treated with high-dose-rate brachytherapy (18 Gy in two fractions) combined with hypofractionated external beam radiation therapy (45 Gy in 15 fractions), the data of 118 consecutive patients followed up for >24 months were prospectively analyzed. The disease-specific quality of life was assessed using the expanded prostate cancer index composite, and the acute genitourinary toxicities were graded based on the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer Toxicity criteria.

Results: The median follow-up duration was 58 months (42–84 months). Thirteen patients (11%) developed Grade 2 or more severe acute genitourinary toxicities. The score for the general urinary domain of the expanded prostate cancer index composite quality-of-life scores dropped significantly at 1 month after high-dose-rate brachytherapy, and then returned to the baseline level by 3 months. Among the dose–volume histogram parameters, the reduction of the expanded prostate cancer index composite quality-of-life scores for the general urinary domain and its subscales at 12 months after high-dose-rate brachytherapy was significantly greater in the patients for whom the V150 or urethral D10 was within the upper 20% of the range than in those in whom the values of these dosimetric parameters were within the lower 20% of the range.

Conclusion: The high-dose area of the prostate gland (V150) or urethra (D10) might influence the quality-of-life scores for the urinary domain and its subscales over the long term.

Key words: HDR brachytherapy, QOL score, acute GU toxicity, hypofractionation
Introduction

With the advances in radiation therapy techniques, there are currently several radiation therapy options for localized prostate cancer, including intensity-modulated radiation therapy, permanent prostate brachytherapy, high-dose-rate brachytherapy (HDR-BT) combined with external beam radiation therapy, etc. (1,2). HDR-BT is one of the most successful methods for delivering a higher dose of radiation to the prostate but not to the surrounding organs, based on its physical properties (3,4). In addition, there is an increasing body of evidence from preclinical and clinical studies supporting a low α/β ratio of prostate cancer relative to the nearby risk organs such as the rectum, and hence potential radiobiological advantages of hypofractionated RT regimens (5,6). HDR-BT is one of the hypofractionated RT regimens, because a relatively large fractional dose is delivered in 1–3 fractions. Theoretically, hypofractionated RT regimens yield similar biological effects as dose escalation. Therefore, HDR-BT combined with external beam radiation therapy, aimed at improvement of the treatment outcomes through dose escalation, is widely accepted as an effective treatment option. In fact, several investigators have reported satisfactory clinical outcomes in high-risk prostate cancer patients receiving HDR-BT combined with external beam radiation therapy (7,8). For assessing the quality of each of the treatment modalities, the quality of life (QOL) is an important factor, besides the incidence of treatment-related toxicities and the oncologic outcomes. There have been few reports of assessment of the QOL after HDR-BT with or without external beam radiation therapy (9,10). In this study, we evaluated the changes in the QOL scores before and after HDR-BT combined with hypofractionated external beam radiation therapy using the expanded prostate cancer index composite (EPIC) as a disease-specific QOL scoring system, and analyzed the correlations between the changes in the QOL scores, especially the scores for the urinary domain and its subscales, and the severity of the acute genitourinary (GU) toxicities caused by the treatment. In addition, we evaluated the correlation between the changes in the disease-specific QOL scores and the dose–volume histogram (DVH) parameters to determine the factors that might affect the disease-specific QOL scores after treatment.

Patients and methods

Patients

Among the patients with localized prostate cancer who were treated with HDR-BT combined with hypofractionated external beam radiation therapy between March 2007 and September 2010 at our institution, 118 consecutive patients in whom the disease-specific QOL was evaluated before and at 1, 3, 6 and 12 months after HDR brachytherapy and who were followed up for at least 24 months were enrolled for this study. All patients had histologically proven prostate adenocarcinoma, and were classified into three risk groups (low-, intermediate- and high-risk) according to the D’Amico risk classification. The risk class distribution in the patients included in this study was as follows: low-risk, 3 patients; intermediate-risk, 20 patients; high-risk, 90 patients. The characteristics of the patients are shown in Table 1.

RT and HDR-BT

All patients were first treated with hypofractionated external beam radiation therapy (10 MV photons, using the six-coplanar field technique) up to 45 Gy in 15 fractions delivered three times a week. The radiation field was limited to the prostate gland ± proximal portion of the seminal vesicle, and none of the patients underwent elective pelvic irradiation. HDR-BT was followed by external beam radiation therapy within 1 or 2 weeks after completion of the external beam radiation therapy. HDR-BT was performed under spinal or local anesthesia at a total dose of 18 Gy delivered in two fractions within 24 h; the minimum interval between the two fractions was 6 h. The contours of the prostate gland, urethra, urinary bladder and rectum were outlined on the transrectal ultrasound (TRUS) images, and the planning target volume (PTV) of HDR-BT was the prostate gland with a margin of 3 to 5 mm; one-third of the seminal vesicles were included in the PTV in the patients with intermediate- or high-risk disease. The prescribed dose of HDR-BT was delivered to the PTV defined above. After the TRUS-based image planning was conducted using the OnCentra Prostate 3.2 (Nucletron, BV), the first treatment session of HDR-BT was conducted using the Nucletron MicroSelectron-HDR, with the patient in the lithotomy position. The dwell times were optimized using the anatomy-based inverse optimization algorithm followed by graphic optimization to obtain optimal coverage of the PTV and reduction of the dose to the organs at risk, including the rectum and urethra. The biologically effective dose (BED) for HDR-BT combined with hypofractionated external beam radiation therapy was 129.1 Gy, assuming that the α/β ratio was 3 Gy, and the equivalent total dose was 78 Gy when the fraction dose was set at 2 Gy administered five times a week. The BED of HDR-BT was calculated using the equation reported by Ng et al. (11).

Hormonal therapy

Patients with intermediate or high-risk disease received neoadjuvant and/or adjuvant androgen deprivation therapy (ADT; LH/antagonist + anti-androgens). In general, patients with intermediate-risk disease received neoadjuvant ADT for 4–6 months without adjuvant ADT, and those with high-risk disease received neoadjuvant ADT for 4–6 months and ADT for 6 months after the completion of HDR-BT combined with hypofractionated external beam radiation therapy. Patients with low-risk disease did not receive any ADT.

Evaluation of toxicity

Acute toxicities were evaluated during the treatment and at every visit after completion of treatment, and all the patients were followed up at 1-month intervals during the first 2 years, and at 3-month intervals thereafter. The acute toxicities caused by HDR-BT combined with hypofractionated external beam radiation therapy were scored in all the patients based on the severity of the symptoms during the follow-up.
period, and graded based on the toxicity criteria of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (12).

Longitudinal evaluation of the QOL
Longitudinal disease-specific health-related QOL evaluation was carried out prospectively, that is, before and at 1, 3, 6, 12 and 24 months after HDR-BT combined with hypofractionated external beam radiation therapy using the EPIC QOL scoring system, in order to assess the time-course of changes and the recovery pattern of the QOL. The EPIC QOL scoring system consists of a 50-item questionnaire categorized into four separate domains (urinary, bowel, sexual and hormonal domains) for quantifying the prostate cancer-specific QOL (13). The urinary domain consists of the following four subscales; urinary function, bother, incontinence and irritation/obstruction. In this study, we focused on the scores for the urinary domains and its subscales up to 12 months after the HDR-BT combined with hypofractionated external beam radiation therapy, in order to evaluate the factors that might affect the incidence of the genitourinary symptoms and changes in the QOL scores in the acute phase after HDR-BT combined with hypofractionated external beam radiation therapy.

Statistics
Comparative analyses between two groups were performed using the unpaired two-tailed t test; P values of <0.05 were considered to denote statistically significant difference.

Results
Clinical outcomes and acute toxicities
The median follow-up duration of all patients included in the analysis was 58 months (range, 42–84 months). At the time of the analysis, nine patients developed biochemical recurrence as defined by the Phoenix definition, and six developed clinical recurrence, including four patients with bone metastasis and two with lymph nodes metastasis. Considering the recurrence pattern and clinical records of the four patients, existence of recurrent disease or diagnosis of biochemical recurrence did not affect the urinary function. Hence, we considered that all patients were suited for evaluation of the correlation between the changes in the QOL scores and the grades of the acute GU toxicities.

With regard to the acute GU toxicities, 13 patients (11%) developed Grade 2 or more severe acute GU toxicities during or after the HDR-BT combined with hypofractionated external beam radiation therapy. Only one patient developed Grade 3 acute GU toxicity, and none developed Grade 4 toxicity. The reason for classification of the acute GU toxicities into Grade 2 or more severe toxicity was the increase in the frequency of nocturia during and after treatment, but the acute reaction recovered in all patients to almost the same level as that prior to treatment. None of the patients had developed urethral stricture by the time of the analysis.

Changes in the QOL scores and the correlations between the QOL scores and the acute toxicities
With regard to the changes in the QOL scores, the EPIC QOL scores for the general urinary domain dropped significantly at 1 month after the HDR-BT as compared with the baseline level, and then recovered gradually to the baseline level by 3 months after the HDR-BT. Longitudinal changes in the EPIC QOL scores for the general urinary domain and its subscales are shown in Fig. 1A–E. The differences in the scores for the general urinary domain and its subscales between the baseline and those measured at 1 month were statistically significant (P < 0.01), but there were no significant differences in the QOL scores between the baseline and those measured at 3 months, indicating that the reduction of the QOL scores at 1 month after the HDR-BT combined with hypofractionated external beam radiation therapy recovered to the baseline level by 3 months after the treatment. The QOL scores for all the subscales also showed the same trend (Fig. 1A; (A) general urinary domain, (B) urinary function, (C) urinary bother, (D) urinary irritation, (E) urinary incontinence). Among the subscales, reduction of the QOL scores for urinary bother and irritation was prominent as compared with that for the other subscales, and the reduction in the QOL score for urinary incontinence was the smallest.

In order to investigate the clinical factors causing significant reduction of the QOL scores for the general urinary domain, we evaluated the HDR-BT DVH parameters, including the prostate D90, V150, urethral maximum dose and urethral D10. Prostate D90 indicates the dose delivered to 90% of the contoured prostate, and urethral D10, the dose delivered to 10% of the contoured urethra. Similarly, prostate V150 denotes the volume of the prostate gland that receives 150% of the prescribed dose. To evaluate the impact of these DVH parameters on the changes in the QOL scores, the patients were divided according to the values of the DVH parameters into those with values in the upper 20% or lower 20% of the range of values, and the differences in the EPIC QOL scores were analyzed between the two groups to assess the impact of the doses to the prostate and organs at risk, including the urethra, on the urinary QOL scores (Figs 2 and 3). Among these factors, reduction of the QOL scores for the general urinary domain at 12 months after the HDR-BT was significantly greater in the patients for whom the prostate V150 or urethral D10 was within the upper 20% of the range than in those in whom the values were within the lower 20% of the range (Figs 2A and 3A). The prostate D90 and maximum urethral dose did not have any significant impact on the reduction of the EPIC QOL score for the general urinary domain. With regard to the changes of the scores for the subscales, the differences in the QOL scores for the subscales, except urinary incontinence, at 12 months after HDR-BT combined with hypofractionated external beam radiation therapy were significant (Figs 2B–E and 3B–E). The degree of reduction of the QOL score for urinary incontinence was almost same between the patients with prostate V150 or urethral D10 values in the upper 20% and lower 20% of the respective ranges. Regarding the correlation between biochemical and clinical recurrence and DVH parameters, the DVH parameters including prostate D90 and V150 were not significantly different between patients who developed recurrence and those who did not.

Discussion
The main advantage of HDR-BT is the high-dose delivery to the target, while keeping the dose to organs at risk, such as the rectum relatively low, due to the high conformity to the prescribed dose in HDR-BT. This enables delivery of higher total doses more safely as compared with that by other modern external beam radiation therapy techniques (14). Based on these physical properties, HDR-BT combined with external beam radiation therapy has been applied, especially for high-risk prostate cancer. Demanes et al. (15) investigated the clinical outcomes of HDR-BT combined with external beam radiation therapy at 10 years after treatment, and reported that the biochemical control rate, overall survival rate and cause-specific survival rate were
90%, 79% and 97%, respectively. Aluwini et al. (16) reported the clinical outcomes of the treatment in 264 hormone-naïve patients with low- and intermediate-risk prostate cancer, and demonstrated that the 7-year actuarial biochemical control rate and overall survival rates were 97% and 91%, respectively.

Concerning the treatment-related toxicities after HDR-BT combined with external beam radiation therapy, several reports have confirmed that the incidence and severities of the acute and late toxicities are within acceptable range despite the high total dose delivery (17,18). However, several clinical and dosimetric factors were associated with the occurrence of severe toxicities. Previously, we demonstrated that the doses to the urethra or rectum were positively correlated with the severity of the GU/gastrointestinal toxicities caused by the HDR-BT combined with hypofractionated external beam radiation therapy (19–22). With regard to the impact of the dosimetric factors on the severity of the GU toxicities, Martinez-Monge et al. also reported that a bladder D50 ≥1.19 Gy was associated with an increased incidence of Grade ≥2 GU toxicity (8). Ghadjar et al. (23) also demonstrated that the urethral V120 (urethral volume receiving ≥120% of the prescribed HDR-BT) was associated with the incidence of acute Grade 2 GU toxicities. The pattern and severity of the acute GU toxicities in this study were almost similar to those reported from other studies, and we consider that the hypofractionated regimen including external beam radiation therapy would not have a negative impact on acute GU toxicities.

As mentioned above, HDR-BT combined with external beam radiation therapy has been established as an effective treatment approach for localized prostate cancer, similar to intensity-modulated radiation therapy or permanent prostate brachytherapy combined with external beam radiation therapy. However, among the modern RT techniques, each has different characteristics, including the overall treatment time and the need for local or spinal anesthesia. This means that evaluation of the quality of treatment based on the clinical outcomes and treatment-related toxicities would be insufficient, especially for a precise comparison of the different RT approaches. Assessment of the severity of treatment-related toxicities is performed according to the grades of the toxicities classified using standardized toxicity criteria, such as the Common Terminology Criteria for Adverse Events.
Toxicities are graded in severity based on the worst grade of symptoms occurring after treatment. In other words, the grading of the toxicities represents the worst grade at a time point after the treatment, and does not reflect the duration or recovery pattern of the toxicities or symptoms. Another approach for assessment of the treatment quality is evaluation of the QOL, indicating that the severity of the treatment toxicities can be reliably assessed by evaluation of the QOL using standardized self-addressed questionnaires. Among the methods used for evaluation of the QOL, longitudinal assessment of the QOL during and after treatment would provide important information regarding the duration of and time to recovery from acute toxicities.

In this study, longitudinal disease-specific health-related QOL was evaluated by prospectively measuring the EPIC QOL scores. As described, the EPIC QOL scoring system consists of a 50-item questionnaire about prostate cancer-specific QOL categorized into four separate domains. This enabled us to evaluate the changes in the disease-specific QOL more precisely as compared with that possible with other QOL scoring systems. Jo et al. (10) reported the results of the changes in the QOL scores using SF-36 and UCLA-PCI, and reported the absence of any significant difference in the SF-36 scale scores between men treated with prostatectomy and those treated with HDR-BT combined with external beam radiation therapy. However, to the best of our knowledge, there has been no report about longitudinal evaluation of the QOL using the EPIC QOL scoring system in patients receiving HDR-BT combined with external beam radiation therapy. The results of this study demonstrated that the EPIC QOL score for the general urinary domain dropped significantly at 1 month after HDR-BT, but returned to the baseline level by 3 months. In addition, we found that the EPIC QOL scores for the general urinary domain and its subscales also dropped at 12 months after the treatment in some patients. Detailed analysis to examine the correlation between the DVH parameters of HDR-BT and the changes in the QOL scores revealed that the reduction of the EPIC QOL scores for
the general urinary domain and its subscales at 12 month was significantly greater in the patients with prostate V150 and/or urethral D10 values within the upper 20% of the range than in those with the values of these parameters within the lower 20% of the range. This indicates that the high-dose areas of the prostate gland and urethra exert influence on the risk of development of late GU toxicity or impairment of urinary function over the long term. Stenmark et al. (24) also demonstrated that the mean dose to the whole and inferior rectum was correlated with the declines in the QOL scores for the bowel domain. In addition, they reported that low (V25–V40), intermediate (V50–V60) and high (V70–V80) doses to the inferior rectum influenced the risk of bleeding, incontinence, urgency and overall bowel problems. Regarding the pattern of toxicity following HDR-BT combined with external beam radiation therapy, Duchesne et al. (25) demonstrated that late toxicity profiles developed after 12 months, typically with low-grade bowel and urinary urgency, the symptoms peaking at 12–24 months, and staying relatively stable subsequently. Based on this finding, reduction of the QOL scores at 12 months after HDR-BT in this study might reflect the onset of late GU toxicities, hence, analysis of the long-term changes of the QOL scores is needed to evaluate the impact of the high-dose area of the prostate gland or urethra in HDR-BT on the late urinary function. In this study, we focused on the changes in the QOL scores in relation to the grades of GU toxicities in the acute phase to clarify the correlations between the acute GU toxicities and the changes in the QOL scores. Actually, we also evaluated the EPIC QOL scores at 2–3 years after the HDR-BT combined with hypofractionated external beam radiation therapy. We propose to report the results regarding the correlation between the dosimetric parameters and the long-term changes in the EPIC QOL scores or late GU toxicities in our next paper, after detailed evaluation of the long-term GU and gastrointestinal toxicities.

Conclusion

The results of this study demonstrated that the acute toxicities after HDR-BT combined with hypofractionated external beam radiation...
therapy were within acceptable range, judging from the changes in the EPIC QOL scores, and the high-dose area of the prostate gland (V150) or urethra (D10) in HDR-BT might exert relatively long-term influence on the QOL scores for the urinary domain and its subscales. Based on these results, further study is needed to confirm the usefulness of long-term evaluation of the EPIC QOL scores and factors affecting the changes in the QOL scores.

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**Conflict of interest statement**

None declared

**References**