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CLINICAL INVESTIGATION **Genitourinary Cancer**

RECTAL BLEEDING AFTER HIGH-DOSE-RATE BRACHYTHERAPY COMBINED WITH HYPOFRACTIONATED EXTERNAL-BEAM RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER: THE RELATIONSHIP BETWEEN DOSE-VOLUME HISTOGRAM PARAMETERS AND THE OCCURRENCE RATE

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Purpose: To determine the predictive risk factors for Grade 2 or worse rectal bleeding after high-dose-rate brachytherapy (HDR-BT) combined with hypofractionated external-beam radiotherapy (EBRT) for prostate cancer using dose–volume histogram analysis.

Methods and Materials: The records of 216 patients treated with HDR-BT combined with EBRT were analyzed. The treatment protocols for HDR-BT were 5 Gy × five times in 3 days or 7 Gy × three, 10.5 Gy × two, or 9 Gy × two in 2 days. The EBRT doses ranged from 45 to 51 Gy with a fractional dose of 3 Gy.

Results: In 20 patients Grade 2 or worse rectal bleeding developed, and the cumulative incidence rate was 9% at 5 years. By converting the HDR-BT and EBRT radiation doses into biologic effective doses (BED), the BED_3 at rectal volumes of 5% and 10% in the patients who experienced bleeding were significantly higher than those in the remaining 196 patients. Univariate analysis showed that a higher rectal $BED_{3-5\%}$ and the use of fewer needles in brachytherapy were correlated with the incidence of bleeding, but $BED_{3-5\%}$ was found to be the only significant factor on multivariate analysis.

Conclusions: The radiation dose delivered to small rectal lesions as 5% is important for predicting Grade 2 or worse rectal bleeding after HDR-BT combined with EBRT for prostate cancer.

High-dose-rate brachytherapy, Rectal bleeding, Hypofractionation, Prostate cancer, Dose–volume histogram analysis.

INTRODUCTION

Recent clinical investigations have estimated the α/β ratio of prostate cancer to be approximately 1.5 to 5.0 Gy (1–6). Although the estimates were based on modeling, the α/β ratios are considered to be lower than those of other cancers. If this is true, hypofractionated radiation therapy (RT) may achieve a better local control rate. Indeed, several recent trials show that hypofractionated RT provides good biochemical control of prostate cancer (7–11).

However, late complications are a great concern during the treatment of prostate cancer. In particular, late rectal toxicities affecting patients' quality of life (12) should be taken into account in addition to local tumor control. To reduce late rectal toxicities, we have given HDR-BT combined with hypofractionated external-beam RT (EBRT) to treat locally advanced prostate cancer since 2001 (13, 14). HDR-BT enables us to deliver a high fractional dose of radiation to a well-defined target volume with rapid fall of the dose outside of the treated area, and it may also provide better local control and reduce the treatment time compared with conventional RT. We previously reported a significant correlation between the incidence of rectal bleeding after HDR brachytherapy combined with EBRT and the rectal volume receiving 10–50% of the prescribed HDR-BT irradiation dose (15). However, we probably failed to detect the true risk factors for rectal bleeding because the results were deduced from (1) the radiation dose regardless of the dose

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Table 1. Patient characteristics

Variable	
Patients (*n*)	216
Median age (y)	68.6 (48.7–84.3)
T stage (AJCC 1997) T1c/T2a/T2b/T3a/T3b	50/47/30/69/20
Gleason Score <6/7/8–10/unknown	23/123/69/1
Initial PSA (ng/ml) <10/≤10-20</≤20	81/75/60
Risk group low/intermediate/high	5/75/136
Hormonal therapy period <2 years/≤2 years	43/173
Diabetes	−/+/unknown 178/37/1
Hemorrhoid	−/+ 172/44
Anticoagulant	−/+ 172/44
Needles for brachytherapy (*n*)	12 (9–18)
Median follow-up time (mo) (range)	35.4 (14.5–77.8)

Abbreviations: AJCC = American Joint Committee on Cancer; PSA = prostate-specific antigen.

fractionation schedule, (2) the small number of study participants ($n = 100$), (3) the relatively short follow-up time (median, 27 months; range, 13–59 months), and (4) the absence of consideration of previously well-known risk factors such as diabetes mellitus and the use of anticoagulants (7, 16). This study was therefore performed with a longer follow-up period and a larger number of patients ($n = 216$), and we used the biologic effective dose (BED) method to convert the HDR-BT dose–volume histogram (DVH) data before subjecting the data to multivariate analysis.

METHODS AND MATERIALS

Patients

Of the 242 patients who underwent ^{192}Ir HDR-BT combined with hypofractionated EBRT at Gunma University Hospital between March 2001 and March 2006, the records of 216 patients with localized prostate cancer who had been followed up for more than 12 months after the completion of treatment were analyzed. The characteristics of the patients are shown in Table 1. None of the patients demonstrated any evidence of lymph node metastasis or distant metastasis. The T stage was classified according to the 1997 American Joint Committee on Cancer/International Union Against Cancer staging criteria.

External beam radiotherapy

The protocol for hypofractionated EBRT has been described previously (7, 17). In brief, RT was administered with 10-MV x-rays. The fractional radiation dose was 3 Gy, and irradiation was performed three times a week. The total dose of EBRT was 51 Gy in 17 fractions for all but 46 patients who received 45 Gy in 15 fractions of EBRT combined with HDR-BT at a fractional dose of 10.5 Gy (Table 2). In this series, the clinical target volume covered the prostate and seminal vesicle region, and the margins of the planning target volume were 5 mm in the posterior direction and 10 mm in all other directions. All treatments were performed by conformal RT according to the oblique four-field technique using multileaf collimators. No patients received elective pelvic RT.

Table 2. Irradiated dose and biologic effective dose for each treatment protocol

Group	EBRT (Gy)	Brachytherapy (Gy)	*n*	BED $\alpha/\beta = 3$	BED $\alpha/\beta = 1.5$
A	51 Gy/17 fx	25 Gy/5 fx	8	139.9	211.3
B	51 Gy/17 fx	21 Gy/3 fx	19	140.7	215.7
C	45 Gy/15 fx	21 Gy/2 fx	46	140.7	221.7
D	51 Gy/17 fx	18 Gy/2 fx	143	141.1	218.5

Abbreviations: EBRT = external beam radiation therapy; BED = biologic effective dose; fx = fractions.

HDR brachytherapy

The HDR-BT was performed 7 to 10 days after the completion of EBRT. The method used for HDR-BT has also been described previously (13, 14). Briefly, with the patient in the lithotomy position under spinal anesthesia, 5-Fr metallic needles were inserted transperineally into the prostate under the guidance of biplanar transrectal ultrasonography. To confirm the position of the urethra, a Nelaton catheter was temporally inserted. After all the needles had been inserted and the catheter had been removed, cystoscopy was performed to adjust the tips of the needles beneath the bladder mucosa. After all the needles had been placed in their optimal positions, a Foley catheter was introduced into the urethra. Thereafter, computed tomography (CT) images were obtained at 2.5- to 5-mm intervals for CT-based treatment planning. The contours of the prostate gland, urethra, bladder, and rectum were delineated on the CT images. The planning target volume for HDR-BT was defined as the prostate gland together with a 2-mm posterior margin and 5-mm margins for all other directions.

After the CT-based planning was conducted by use of the Nucletron Planning System (Nucletron, BV, Veenendaal, The Netherlands), the first HDR-BT session was administered by use of the Nucletron MicroSelectron-HDR ^{192}Ir-remote afterloading system (Nucletron, BV). Dwelling positions were located at 2.5-mm intervals along each catheter, and the dose distribution was manually optimized to cover the prostate gland and avoid the rectum and urethra according to a geometric optimization algorithm.

At our institution, we have adopted hypofractionated EBRT using a fractional dose of 3 Gy administered three times weekly for the treatment of localized prostate cancer (17). We determined the dose fractionation schedule for HDR-BT combined with EBRT on the basis of the BED (18). To calculate the BED for combined therapy, we adopted the method using the dose-modifying factor reported by Nag and Gupta (19), although their calculations were based on a model and might have some uncertainty. Inasmuch as both methods had equal occurrence rates of late side-effects, we designed the schedule to use α/β ratios of 3 Gy that re usually used for late-responding normal tissue (18, 19). The fractional doses and the number of fractions used in HDR-BT were prospectively altered as follows: 5 Gy × five times (Group A), 7 Gy × three times (Group B), 9 Gy × two times (Group C), and 10.5 Gy × two times (Group D). In each fractionation schema, the first treatment session was conducted on the same day as implantation, and the subsequent treatment sessions were performed twice daily on subsequent days. Thus, the treatment duration was 3 days for the 5 Gy × five times schedule and 2 days for the remaining schedules.

Hormonal therapy

All patients initially received androgen deprivation therapy (ADT), which was continued during and after RT. ADT consisted