Acute and late toxicities in localized prostate cancer patients treated with low-dose $^{125}$I brachytherapy (110 Gy) in combination with external beam radiation therapy versus brachytherapy alone (160 Gy)

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Abstract

**Purpose:** The aim of this analysis was to compare acute and late toxicities between low-dose-rate brachytherapy (LDR-BT) (110 Gy) in combination with 45 Gy in 25 fractions external beam radiation therapy (EBRT) and LDR-BT (160 Gy) alone for localized prostate cancer.

**Material and methods:** One hundred five consecutive patients with localized prostate cancer treated from May 2014 to May 2017 were included in this retrospective analysis. Sixty patients received combination therapy and 45 patients received BT monotherapy. The LDR-BT procedure was performed using $^{125}$I seeds.

**Results:** The median follow-up time was 28 months in both groups. Three-year effect rates were overall survival: 100% in both groups. The biochemical failure rate was 2.3% in the combination group and 0% in the monotherapy group ($p = 0.373$). No patients died during the study period. In both groups, almost all the patients experienced acute urethritis. There was a significant difference between the combination therapy group (8.3%) and BT monotherapy group (11.1%) in late genitourinary (GU) toxicities ≥ grade 2 ($p = 0.035$). Only 2 patients (3.3%) in the combination therapy group developed late ≥ grade 2 rectal hemorrhage. There were no significant differences between two groups in hematuria ≥ grade 2 ($p = 0.068$) or rectal hemorrhage ≥ grade 2 ($p = 0.206$).

**Conclusions:** To our knowledge, this is the first report to compare the GU and gastrointestinal toxicities between the combination therapy and BT monotherapy (160 Gy) for localized prostate cancer. Unexpectedly, there were more late GU toxicities (except for hematuria) in the BT monotherapy group.

**Key words:** low-dose-rate brachytherapy, prostate cancer, radiation therapy, toxicity.

Purpose

Patients with low-risk clinically localized prostate cancer are confronted with multiple curative treatment options such as radical prostatectomy (RP), low-dose-rate brachytherapy (LDR-BT) as monotherapy, definitive external beam radiation therapy (EBRT) using three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and active surveillance (AS) [1,2].

Low-dose-rate BT has been shown to be an acceptable, effective, and safe therapy for localized prostate cancer [3]. This approach has lower complications and is less invasive than RP. In comparison with EBRT, LDR-BT can deliver higher dose with lower exposure to organs at risk. It is relatively well-tolerated by elderly patients because seed insertion can be completed under general or spinal anesthesia in a few hours.

In some institutions, LDR-BT is initiated in an outpatient setting or during a brief hospital stay, after which patients can be discharged some hours after treatment [4]. Most patients may return to work and perform normal activities within a few days after the treatment. This makes...
it an attractive option for patients in terms of convenience and minimal interference with daily activity and lifestyle.

Recently, LDR-BT has been found to be adaptable to include a dose escalation or to being combined with EBRT to supply a boost. Although there is room for interpretation, some reports have implied that dose escalation may improve results [5,6]. At our institution, low-risk patients have been prescribed 145 Gy in LDR-BT. Intermediate-risk and intermediate-tier high-risk (intermediate-to-high-risk) patients have been managed with dose escalation LDR-BT prescribed 160 Gy, or with LDR-BT in combination with EBRT (3D-CRT or IMRT).

As mentioned above, LDR-BT has the great advantage of minimal interference with lifestyle. It is important to choose LDR-BT methods not only considering the remaining life expectancy but also comorbidity, age at diagnosis, and quality of life (QOL).

Both the negative effects of the treatment and possible effects on QOL should be considered in the decision-making process. The aim of this analysis was to compare the acute and late toxicities between LDR-BT (110 Gy) in combination with EBRT and LDR-BT (160 Gy) as monotherapy for localized prostate cancer.

**Material and methods**

**Patients**

From May 2014 to May 2017, 105 consecutive locally advanced prostate cancer patients were treated with LDR-BT (160 Gy) as BT monotherapy (the monotherapy group) or LDR-BT (110 Gy) in combination with EBRT (the combination therapy group).

Of the 105 patients, 60 patients received combination therapy and the remaining 45 patients received BT monotherapy.

### Table 1. Patient and treatment characteristics

|                | Combination therapy group | BT monotherapy group | P value |
|----------------|---------------------------|----------------------|---------|
| The number of patients | 60                        | 45                   |         |
| Age (years)    |                           |                      |         |
| Median         | 68 (range: 44-81)         | 68 (range: 53-81)    | 0.99    |
| PS (ECOG)      |                           |                      |         |
| 0              | 57                        | 41                   | 0.34    |
| 1              | 3                         | 3                    | (PS = 0) |
| 2              | 0                         | 1                    |         |
| Clinical stage (TNM Classification of Malignant Tumors, 8th edition) | < 0.001 |
| Stage I        | 20                        | 29                   |         |
| Stage II       | 32                        | 16                   |         |
| Stage III      | 8                         | 0                    |         |
| Initial PSA (ng/ml) |                     |                      | 0.08    |
| Median         | 9 (range: 4-54.6)         | 7.46 (range: 4-20.6) |         |
| < 10           | 38                        | 33                   |         |
| 10-20          | 16                        | 10                   |         |
| ≥ 20           | 6                         | 2                    |         |
| Gleason score  |                           |                      | < 0.001 |
| 4 + 5 = 9      | 4                         | 0                    |         |
| 4 + 4 = 8      | 20                        | 5                    |         |
| 4 + 3 = 7      | 13                        | 11                   |         |
| 3 + 4 = 7      | 20                        | 19                   |         |
| 3 + 3 = 6      | 3                         | 10                   |         |
| Number of positive cores | 4/12 core (30%) | 3/12 core (20%) | < 0.001 |
| NCCN risk classification criteria | < 0.001 |
| High           | 34                        | 7                    |         |
| Intermediate   | 25                        | 35                   |         |
| Low            | 1                         | 3                    |         |

*BT – brachytherapy; PS – performance status; ECOG – Eastern Cooperative Oncology Group; PSA – prostate-specific antigen; NCCN – National Comprehensive Cancer Network*
monotherapy. We retrospectively reviewed the medical records. Determination of the clinical stage was based on physical examination, chest X-ray, chest-pelvic computed tomography (CT), pelvic magnetic resonance imaging (MRI), and bone scan.

All patients were examined before treatment by urologists and radiation oncologists, and they were classified according to the International Union Against Cancer staging system and categorized according to the National Comprehensive Cancer Network (NCCN) risk classification criteria (TNM Classification of Malignant Tumors, 8th edition). The disease characteristics of the 105 patients are summarized in Table 1. All patients had pathologically confirmed adenocarcinoma and underwent Gleason score histological grading.

This study was approved by the institutional review board (B180700026), and informed consent was obtained from all patients prior to treatment.

**Methods of LDR-BT**

The LDR-BT procedure was performed at our institution using 125I seeds (Onco-Seed®, Nihon Medi-physics, Kobe, Japan). The target volume of the implant was the prostate gland and the implantation was based on intraoperative planning with real-time dynamic dose calculation using commercial software (VariSeed®, Varian Medical Systems, Palo Alto CA, USA). Implantation was performed under general anesthesia using real-time transrectal ultrasound (TRUS) and a standard template, and the seeds were individually deposited using a Mick applicator. The LDR-BT constraints are shown in Table 2. All patients underwent chest and pelvic radiography just after the implantation to assess seed distribution in the prostate and to detect seed migration.

**Post-dosimetric evaluation**

Both post-implant CT and MRI were obtained, and post-implant dosimetric study was performed approximately 3 weeks after the LDR-BT. The biologically effective dose (BED) at the post-plan D90 was calculated using an α/β ratio = 2. The total BED for the combination therapy group was a sum of the BEDs from the LDR-BT and that from the EBRT [7] (Table 3).

**External beam radiation therapy**

In the combination therapy group, the planning CT was obtained approximately one month after the LDR-BT. In this group, patients received 45 Gy in 25 fractions using a four-field box technique with 15 MV 3D-CRT or IMRT using TomoTherapy system (Accuray Inc., Sunnyvale, CA).

The clinical target volume (CTV) consisted of the whole prostate and the proximal one-third of the seminal vesicles (SV). PTV was defined as the CTV with a 3-5 mm expansion margin posteriorly, and 8-10 mm expansion margins inferiorly, superiorly, anteriorly, and laterally. The maximum allowable dose delivered to the PTV was 107% of the prescribed dose, and the minimum allowable dose delivered to the PTV was 95% of the prescribed dose. The dosimetric goals to the rectum were: V10 < 20% (no more than 20% of the rectal volume should receive > 40 Gy), and V30 < 30% and V50 < 40%. The maximum acceptable dose delivered to the bladder was < 110% of the prescribed dose.

**Evaluation criteria and statistical analysis**

The patients were followed up 3-6 months after the treatment. During these visits, serum PSA levels and toxicity data were collected.

Comparison of clinical variables between the two groups was performed using Mann-Whitney’s U-test. The

| Table 2. Low-dose-rate brachytherapy constraints |
|------------------------------------------------|
|                | Combination therapy group | BT monotherapy group |
|----------------|---------------------------|----------------------|
| BT prescribed dose | 110 Gy                     | 160 Gy               |
| Prostate        |                           |                      |
| D90            | ≥ 110 Gy (> 100%)          | 180-200 Gy           |
| V100           | ≥ 95%                      |                      |
| V150           | ≤ 60%                      | ≤ 150%               |
| Urethra         |                           |                      |
| U V150         | = 0 cc (165 Gy)            | ≤ 10%                |
| R U D10        | < 130%                     | ≤ 150%               |
| Rectum         |                           |                      |
| R V100         | ≤ 0.1 cc                   | ≤ 1 cc               |
| R D2 cc        | ≤ 110 Gy                   |                      |

Table 3. The total biologically effective dose (BED) at implant phase and post-implant phase

|                         | Combination therapy group | BT monotherapy group |
|-------------------------|---------------------------|----------------------|
| Implant phase           |                           |                      |
| BED (α/β = 2)           | 211.1                     | 191.8                |
| EQD2                    | 106 Gy                    | 96 Gy                |
| Post-implant phase      |                           |                      |
| BED (α/β = 2)           | 220.6                     | 209.6                |
| EQD2                    | 110 Gy                    | 104 Gy               |

BT – brachytherapy; D90 – dose received by 90% of the prostate volume; V100 – volume of prostate receiving 100% of the prescribed dose; V150 – volume of prostate receiving 150% of the prescribed dose; U V150 – volume of urethra receiving 150% of the prescribed dose; U D10 – dose received by 10% of the urethra volume; U D150 – dose received by 150% of the urethra volume; R V100 – volume of rectum receiving 100% of the prescribed dose; R D2 cc – dose received by 2 cc of the rectum volume.
Results

The median follow-up time was 28 months (range: 11-48 months) in the combination therapy group, and 28 months (range: 12-48 months) in the BT monotherapy group.

The treatment characteristics of the study group are summarized in Table 4. Seed migrations were observed (combination therapy group/BT monotherapy group) in the lung (n = 3/4 = 5), pelvis (n = 8/14 = 15), seminal vesicle (n = 6/14 = 6), and other sites (n = 17/14 = 2). Table 3 also shows the post-implant data of the study groups. CT data could not be obtained in 3 patients; 102 patients were analyzed in the post-implant phase.

In the combination therapy group, the median EBRT duration time was 35 days (range: 32-41), and the du-

Table 4. The treatment characteristics at implant phase and post-implant phase

|                           | Combination therapy group | BT monotherapy group | P value |
|---------------------------|---------------------------|----------------------|---------|
| **Table of Values**       |                           |                      |         |
| Median follow-up time (months) | 28 (range: 11-48) | 28 (range: 12-48) | NS      |
| The days from diagnosis to BT (days) | 136.5 ±287.75 | 69 ±173.26 | 0.939   |
| Anticoagulant drug (n)     | 6                         | 6                    | NS      |
| **Implant phase**          |                           |                      |         |
| Seeds number (n)           | 60 (range: 35-75)         | 80 (range: 55-100)  | 0.001   |
| Migrations (n)             | 0.4 ±0.7                  | 0.7 ±0.9             | 0.06    |
| D90 (Gy)                   | 129.3 ±5.6                | 196.2 ±6.5           | < 0.001 |
| Activity (mCi)             | 0.33 (range: 0.26-0.35)   | 0.33 (range: 0.33-0.35) |         |
| Prostate volume at implant (cc) | 27.7 ±7.7                | 27.5 ±6.5            | 0.74    |
| R V100 (cc)                | 0.08 ±0.2                 | 0.2 ±0.3             | < 0.001 |
| R D2 cc (Gy)               | 73.1 ±7.7                 | 109.3 ±12.5          | < 0.001 |
| R D15 (Gy)                 | 68.2 ±6.9                 | 110.3 ±15.1          | < 0.001 |
| U V150 (cc)                | 0 ±0.02                   | 0 ±0.12              | 0.02    |
| U D50 (Gy)                 | 89.2 ±18.6                | 114.8 ±28.7          | < 0.001 |
| U D10 (Gy)                 | 136.0 ±6.7                | 200.8 ±8.3           | < 0.001 |
| **Post-implant phase**     |                           |                      |         |
| CT not available           | 1                         | 2                    |         |
| Prostate volume            | 28.9 ±7.2                 | 27.3 ±6.0            | 0.426   |
| D50 post (Gy)              | 120.4 ±9.3                | 180.4 ±14.9          | < 0.001 |
| R V100 post (cc)           | 0.2 ±0.2                  | 0.3 ±0.3             | 0.098   |
| R D2 cc post (Gy)          | 70.7 ±10.3                | 103.4 ±17.4          | < 0.001 |
| R D50 cc post (Gy)         | 35.6 ±8.1                 | 49.4 ±12.8           | < 0.001 |
| U V150 cc post (cc)        | 0.01 ±0.5                 | 0.01 ±0.4            | 0.15    |
| U D50 cc post (Gy)         | 90.1 ±17.0                | 126.0 ±29.7          | < 0.001 |
| U D10 cc post (Gy)         | 138.2 ±10.7               | 208.0 ±14.8          | < 0.001 |

BT – brachytherapy; NS – not significant; D90 – dose received by 90% of the prostate volume; R V100 – volume of rectum receiving 100% of the prescribed dose; R D2 – dose received by 2 cc of the rectum volume; R D50 – dose received by 50% of the rectum volume; U V150 – volume of urethra receiving 150% of the prescribed dose; U D50 – dose received by 50% of the urethra volume; U D10 – dose received by 10% of the urethra volume; CT – computed tomography
Combination therapy of LDR-BT versus LDR-BT alone for prostate cancer

Hematuria and rectal hemorrhage (grade 1-2) frequently developed in the combination therapy group: hematuria, n = 5 (8.3%); rectal hemorrhage, n = 17 (28.3%). Whereas, in the monotherapy group, there was no hematuria and only one patient developed grade 1 rectal hemorrhage. There was no significant difference between two groups in hematuria ≥ grade 2 (p = 0.068) and in rectal hemorrhage ≥ grade 2 (p = 0.206).

Discussion
To our knowledge, this is the first report to compare the acute and late toxicities between 125I LDR-BT 110 Gy in combination with EBRT and 125I LDR-BT 160 Gy as monotherapy for localized prostate cancer.

There have been several reports to compare the treatment outcomes and GU or GI toxicities [8,9,10,11,12,13,14]. However, they included a variety of LDR-BT modalities or sources, or different prescribed doses such as mixed 125I and 103Pb [8,15,16]. In one study, the LDR-BT procedure included both pre-operative planning and intra-operative planning [12], and in another only pre-operative planning was used [8]. The prescribed dose of LDR-BT was not uniform, ranging from 137-160 Gy [8,12,13].

In this study, LDR-BT used only 125I, the prescribed dose was only 160 Gy in monotherapy and 110 Gy in combination therapy, and all LDR-BT was intraoperatively planned. The treatment had high uniformity. In addition, most previous reports targeted low-to-intermediate-risk prostate cancer patients, whereas ours focused on localized intermediate-to-high-risk patients.
Almost all patients (99%) sustained acute grade 2 GU toxicities, a higher incidence compared with previous reports [2,10]. However, in our study, they were categorized as grade 2 GU because they were medicated for urinary symptoms.

It was similar to previous reports that there were no acute GI toxicities ≥ grade 2 [12]. As we mentioned above, the variety of LDR-BT procedures used in prior studies makes comparison difficult.

In this study, late GU toxicities ≥ grade 2 in the combination therapy group showed a rate of 8.3% and the BT monotherapy group 11.1%. In the previous reports of BT monotherapy, the late GU toxicity rate was 8.1-22.3% [17,18], and late urinary retention was reported in 0.6% [4]. By contrast, a study of BT and EBRT combination therapy reported a late GU grade 2 toxicity rate of 17% and grade 3 - 3% [10]. The GU toxicity rate was similar to previous reports in both groups. In this study, late grade 2 GU toxicity was significantly higher in the BT monotherapy group (p = 0.035). With regard to bladder catheterization, in our study, only one patient (2.2%) in the BT monotherapy group required long-term bladder catheterization. There have been some reports of rates of the need for bladder catheterization between 0.2-6.1% [4,18,19] for acute GU toxicity in BT monotherapy.

In this study, 2 patients (3.3%) in the combination therapy group, developed rectal hemorrhage as late grade 2 GI toxicity. It was comparable to previous reports of late grade 2 GI toxicity rates of 0.3-1.3% [3,18] in BT monotherapy studies, and 2.8-6.8% [8,12] in the studies including EBRT combination therapy.

There was a significant difference between EBRT combination therapy and BT monotherapy in late GU and GI toxicity rates in one study [12]; estimated G2 rectal bleeding with monotherapy was 18% and 22% with combined therapy in another report [13]. In studies of HDR-BT, HDR-EBRT combination therapy was associated with a higher rate of bleeding than HDR-BT mono-

### Table 5. Acute and late toxicities

|                          | Combination therapy group | BT monotherapy group |
|--------------------------|---------------------------|----------------------|
|                          | Grade 1 | Grade 2 | Grade ≥ 3 | Grade 1 | Grade 2 | Grade ≥ 3 |
| **Acute toxicities**     |          |         |           |          |         |           |
| GU                       |          |         |           |          |         |           |
| Urethritis               | 1        | 59      | 0         | 0        | 45      | 0         |
| Urinary urgency          | 45       | 0       | 0         | 23       | 0       | 0         |
| Urinary incontinence     | 6        | 0       | 0         | 4        | 2       | 0         |
| Urinary retention        | 2        | 0       | 0         | 1        | 0       | 0         |
| Urinary tract pain       | 19       | 0       | 0         | 13       | 0       | 0         |
| Hematuria                | 0        | 0       | 0         | 1        | 0       | 0         |
| GI                       |          |         |           |          |         |           |
| Proctitis                | 4        | 0       | 0         | 0        | 0       | 0         |
| Diarrhea                 | 3        | 0       | 0         | 3        | 0       | 0         |
| Anal pain                | 23       | 0       | 0         | 5        | 0       | 0         |
| **Late toxicities**      |          |         |           |          |         |           |
| GU                       |          |         |           |          |         |           |
| Urinary urgency          | 2        | 0       | 0         | 10       | 1       | 0         |
| Urinary incontinence     | 1        | 2       | 0         | 4        | 2       | 0         |
| Urinary retention        | 0        | 0       | 0         | 0        | 1       | 0         |
| Urinary tract pain       | 1        | 2       | 0         | 5        | 3       | 0         |
| Hematuria                | 1        | 3       | 1         | 0        | 0       | 0         |
| GI                       |          |         |           |          |         |           |
| Proctitis                | 10       | 0       | 0         | 0        | 0       | 0         |
| Anal pain                | 1        | 0       | 0         | 1        | 0       | 0         |
| Rectal hemorrhage        | 15       | 2       | 0         | 1        | 0       | 0         |

BT – brachytherapy; GU – genitourinary; GI – gastrointestinal
therapy [20]. In our study, there was a high incidence of rectal hemorrhage and hematuria in the combination therapy group; however, there were no significant differences between the two groups in hematuria ≥ grade 2 (p = 0.068) or in rectal hemorrhage ≥ grade 2 (p = 0.206), respectively. We also analyzed the relationship between antiocoagulant medicine use and bleeding, and found no significant association. There have been no reports about it in combination therapy vs. BT monotherapy. In BT monotherapy, there has been one report of a late hemorrhage rate of 15.4% [17], and several reports of late rectal hemorrhage rates of 6-16% [3,4,17]. In our study, only one late grade 1 rectal hemorrhage in the monotherapy group was recorded.

We analyzed the 3D-CRT and IMRT groups in combination therapy group but found no significant differences between them in late GU toxicity (p = 0.13). The failure to reach statistical significance is likely attributable to the small patient numbers (only nine patients received IMRT).

The treatment outcome was excellent in this study and at the same time, it may be meaningless because of short period of observation.

The American Brachytherapy Society guidelines (2012) characterize BT and EBRT combination therapy as an option, and recommend it for high-risk disease [8,12]. In the American Society of Clinical Oncology (ASCO) guidelines [21] for low-intermediate risk patients, Gleason score (GS) 7 and PSA < 10, GS 6 and PSA 10-20, LDR-BT may be offered as monotherapy. Additionally, the NCCN guidelines also state that BT and EBRT combination therapy is optional. Recently, several reports on BT and EBRT combination therapy found no difference in the survival of prostate cancer patients [8,13,22,23] compared with BT monotherapy. Stones et al. reported, even at a high grade, if the tumor was confined to the prostate gland, BT only is adaptive, but there are also reports with opposite results [9,10,24,25,26].

Conversely, an EBRT boost may be indispensable when there is suspicion of incipient extracapsular or seminal vesicle invasion seen on MRI. We predict that dose escalation for BT monotherapy may be less toxic. Our results show significantly less GU toxicity with combination therapy. Although the definite indications of EBRT combination therapy have not been established, it may be useful for patients with increased risk of GU toxicity.

LDR-BT monotherapy has a great benefit compared to EBRT such as: 1. Higher dose can deliver to prostate with lower exposure to organs at risks; 2. The treatment time became remarkably shorter than EBRT because usually the insertion was completed within one day [14,19,27]. In comparison with EBRT, LDR-BT can deliver a higher dose with lower exposure to organs at risk.

In this study of intermediate-to-high-risk prostate cancer patients, there was no significant difference in BRFS between the combination therapy group and BT monotherapy group (p = 0.373). If there is no apparent invasion outside of the prostate, the dose escalation BT monotherapy may be a good treatment option for intermediate-to-high-risk prostate cancer patients who are elderly, taking anticoagulants, or who cannot follow a schedule of external beam treatments, as long as they understand slightly increased risk of GU toxicities.

The limitations of this study include its retrospective nature, the relatively short follow-up time, and the small number of patients. Further studies are needed to evaluate the long-term prognosis.

Conclusions

To our knowledge, this is the first report to compare the GU and GI toxicities between 125I LDR-BT 110 Gy in combination with EBRT and 125I LDR-BT 160 Gy as monotherapy for localized prostate cancer. In this study, we found significantly higher grade 2 GU toxicity in the BT monotherapy group. It is important to choose a treatment method according to the characteristics of the patient, since there are many treatment options for localized prostate cancer.

Disclosure

Authors report no conflict of interest.

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