Original paper

High biologically effective dose radiation therapy using brachytherapy in combination with external beam radiotherapy for high-risk prostate cancer

Keisei Okamoto, MD, PhD[1], Akinori Wada, MD[2], Naoaki Kohno, MD, PhD[3]

[1]Department of Brachytherapy for Prostate Cancer, [2]Department of Urology, [3]Department of Radiology, Shiga University of Medical Science, Shiga, Japan

Abstract

Purpose: To evaluate the outcomes of high-risk prostate cancer patients treated with biologically effective dose (BED) ≥ 220 Gy of high-dose radiotherapy, using low-dose-rate (LDR) brachytherapy in combination with external beam radiotherapy (EBRT) and short-term androgen deprivation therapy (ADT).

Material and methods: From 2005 to 2013, a total of 143 patients with high-risk prostate cancer were treated by radiotherapy of BED ≥ 220 Gy with a combination of LDR brachytherapy, EBRT, and androgen deprivation therapy (ADT). The high-risk patients in the present study included both high-risk and very high-risk prostate cancer. The number of high-risk features were: 60 patients with 1 high-risk factor (42%), 61 patients with 2 high-risk factors (43%), and 22 patients with 3 high-risk factors (15%) including five N1 disease. External beam radiotherapy fields included prostate and seminal vesicles only or whole pelvis depending on the extension of the disease. Biochemical failure was defined by the Phoenix definition.

Results: Six patients developed biochemical failure, thus providing a 5-year actual biochemical failure-free survival (BFFS) rate of 95.2%. Biochemical failure was observed exclusively in cases with distant metastasis in the present study. All six patients with biochemical relapse had clinical failure due to bone metastasis, thus yielding a 5-year freedom from clinical failure (FFCF) rate of 93.0%. None of the cases with N1 disease experienced biochemical failure. We observed four deaths, including one death from prostate cancer, therefore yielding a cause-specific survival (CSS) rate of 97.2%, and an overall survival (OS) rate of 95.5%.

Conclusions: High-dose (BED ≥ 220 Gy) radiotherapy by LDR in combination with EBRT has shown an excellent outcome on BFFS in high-risk and very high-risk cancer, although causal relationship between BED and BFFS remain to be explained further.

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Key words: LDR brachytherapy, high-risk, prostate cancer, seeds.

Purpose

High-risk prostate cancer is a category of prostate cancer that includes an aggressive tumor and/or a high tumor burden [1,2]. Importantly, inadequate local control in the management of the high-risk prostate cancer patients leads to metastasis or death. Therefore, for optimal radiotherapy results in high-risk prostate cancer, a good local control by dose escalation is crucial [1,3].

The use of prostate brachytherapy provides the advantage of safe delivery of a high biologically effective dose (BED) to the prostate [1,2,3,4]. The advantage of combination therapy with low-dose-rate (LDR) brachytherapy and external beam radiotherapy (EBRT) has been recently confirmed by the ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) randomized trial [5]. The combination of LDR and EBRT is associated with prostate cancer specific mortality in some prostate cancer patients [6]. In terms of radiation dose, Stone *et al*. have shown that patients with Gleason 8-10 disease receiving a biologically effective dose (BED) ≥ 220 Gy by combination therapy with LDR brachytherapy and EBRT, obtained improvement in biochemical failure-free survival (BFFS) [7]. In order to study the efficacy and toxicity of the combination therapy of BED ≥ 220 Gy by tri-modality (LDR brachytherapy in combination with EBRT and short term androgen deprivation therapy [ADT]) in a Japanese population, we analyzed the clinical outcome of 143 high-risk and very high-risk patients, including those with N1 disease.

Address for correspondence: Prof. Keisei Okamoto, MD, PhD, Department of Brachytherapy for Prostate Cancer, Shiga University of Medical Science, Otsu, Shiga, 520-2192, Japan, phone: +81 77-548-2993, fax: +81 77-548-2993, ✉ e-mail: keisei@belle.shiga-med.ac.jp

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Material and methods

Patients

This retrospective and observational research has been conducted in accordance with the Helsinki Declaration. This study has been approved and monitored by our institutional ethics committee (Shiga University of Medical Science: 23-133 and 23-196). For individual data usage including images, we have obtained separate informed consent from patients. From 2005 to 2013, a total of 143 patients with high-risk prostate cancer were treated by a combination of LDR brachytherapy, external beam radiotherapy, and ADT. These patients had a minimum follow-up time of two years. The high-risk patients in the present study included both high-risk and very high-risk prostate cancer as classified in the current National Cancer Network Criteria (http://www.nccn.org). Briefly, patients were defined as high-risk if they fulfilled at least one of the following criteria: prostate-specific antigen (PSA) level higher than 20 ng/ml, and/or Gleason score > 8, and/or clinical stage T3. We also enrolled T3b-T4 disease in this study. Gleason scores of all biopsy specimens were reviewed by our central pathologist before the treatment. Clinical T stage was determined by a combination of magnetic resonance imaging (MRI) and digital examination. All patients had bone scans and computed tomography (CT) of the pelvis to check the presence of bone metastasis and lymph node metastasis.

In addition, we enrolled regional N1 disease patients in this study if the nodal involvement of the pelvis was limited (one or two nodal metastases). Lymph node metastasis was finally confirmed on CT by shrinkage of lymph nodes through neoadjuvant ADT. Clinical characteristics of the patients (PSA, Gleason score clinical T stage) in the present study is shown in Table 1. The distribution of the number of high-risk factors in the present study is shown in Table 2.

Table 1. Patient characteristics

Variable	*n* = 143 (%)
Age, years	
Median (range)	66.9 (55-82)
PSA at diagnosis, ng/ml	
< 10	41 (29%)
10-20	43 (30%)
> 20	59 (41%)
Median (range)	20.76 (4-130)
Gleason score	
6	6 (4%)
7	41 (29%)
8	68 (48%)
9	25 (17%)
10	3 (2%)
Tumor stage	
T1c	13 (9%)
T2a	4 (3%)
T2b	24 (17%)
T2c	11 (8%)
T3a	70 (48%)
T3b	20 (14%)
T4	1 (1%)
Metastasis	
No metastasis	138 (97%)
Regional lymph node metastasis	5 (3%)

PSA – prostate specific antigen

Treatment

All patients were treated by combination therapy with LDR brachytherapy, EBRT, and ADT. Androgen deprivation therapy included neoadjuvant (six months) and adjuvant (six months) settings across the seed implantation. Androgen deprivation therapy consisted of gonadotropin-releasing hormone agonist injection and anti-androgen. Low-dose-rate brachytherapy implantation in the prostate was conducted with ^{125}I seeds using real-time ultrasound guided technique [8]. Radioactive seeds were deposited into the prostate using a Mick applicator (Mick Radio-Nuclear Instruments, Inc., Mount Vernon, NY, USA). Seminal vesicle implantation was added based on the advancement of the disease such as seminal vesicle involvement or tumor location adjacent to the seminal vesicle [9]. The prescription dose of seed implantation was set at 110 Gy [3].

To achieve a BED of 220 Gy, D_{90} of 130 Gy have to be delivered (post-implant D_{90}) by using ^{125}I seed implantation in combination with the 45 Gy of EBRT in 1.8 Gy fraction [3]. In order to secure 130 Gy of D_{90} at post ^{125}I seed implantation, we usually set D_{90} at implantation from 135 Gy to 145 Gy.

By complying with the above-mentioned implantation policy, the clinical target volume (CTV) was covered with 130 Gy, and the CTV with margin was covered with 110 Gy (prescription dose).

Post-implant dosimetry with CT and MRI guidance was carried out at one month after seed implantation. Supplemental EBRT was delivered four to eight weeks after seed implantation. External beam radiotherapy consisted of a median dose of 45 Gy, given in 1.8 Gy fractions via a three-dimensional conformal technique. Clinical target volume was designed as the entire prostate and

Table 2. Number of high-risk factors

1	60 (42%)
2	61 (43%)
3	22 (15%)

seminal vesicle. Planning target volume (PTV) included CTV-block with a 15 mm margin, except at the prostato-rectal interface where 7-10 mm margin was used.

For each case, the BED was calculated from the prostate D_{90} and EBRT dose using the formula described previously [4]: the EBRT dose was determined, so that the total BED would be higher than 220 Gy as long as UD_{30} and R_{100} were tolerable. Upon supplemental EBRT, whole pelvis external beam radiotherapy (45 Gy) was applied in N1 cases or in some of the very high-risk patients, although the usual EBRT fields included prostate and seminal vesicles only with margin.

Toxicity

Acute toxicity was defined if symptoms developed within the first year after seed implantation. Late toxicity was defined if any kind of symptom developed after one year, or if a symptom occurred within the first year and persisted for more than one year. Toxicity was recorded by the Common Terminology Criteria for Adverse Events version 4.0.

Follow-up and statistical analysis

Scheduled follow-up was done by PSA blood test and physical examination every three months for the first two years, followed by every six months thereafter. Duration of follow-up was calculated from the end of the supplemental EBRT. Patients had a minimum follow-up time of two years (median 52 months; range, 28-131 months). Actuarial survival curves were calculated by the Kaplan Meier method to determine biochemical relapse-free survival (BFFS), freedom from clinical failure (FFCF) survival, cause-specific survival (CSS), and overall survival (OS). Biochemical failure was defined according to the Phoenix Definition [9]. The criterion for biochemical failure with subsequent PSA decrease to < 0.5 ng/ml without intervention was categorized as a benign bounce and was excluded from the biochemical failure group. Upon a true biochemical failure, we performed CT, MRI, bone scan, and rectal digital examination to evaluate whether biochemical failure was caused by distant metastasis or local failure. Biochemical relapse-free survival was calculated for all living patients and reflected biochemical failures. Freedom from clinical failure survival rate was calculated for all living patients and presented clinical failure events (local, regional, and distant failure). Cause-specific survival reflected prostate cancer-specific death. Overall survival presented all deaths, cancer related or unrelated.

Results

Dosimetric parameters and biologically effective dose

Dosimetric parameters of seed implantation at one month and total BED of 143 high-risk patients are shown in Table 3. Total BED was over 220 Gy in 106 cases (74%), over 215 Gy in 119 cases (83%), over 210 Gy in 128 cases (90%), over 205 Gy in 131 cases (92%), and over 200 Gy in 136 cases (95%) (Table 4).

Efficacy of the treatment

Of the 143 high-risk patients, six developed PSA failure, yielding an actuarial BFFS rate of 95.2% at 5 years (Figure 1). These six patients with BFFS had a clinical failure due to bone metastasis, yielding a FFCF rate of 93.0% at 5 years (Figure 1). According to MRI and rectal digital examination, all six patients with biochemical failure and clinical failure had no evidence of local failure. One of these patients with biochemical failure and clinical failure died of prostate cancer, yielding a CSS rate of 97.2% at 5 years (Figure 1). Another three patients died during follow-up, including two patients who died of cerebral infarction, and one patient who died of myelodysplastic syndrome, yielding an OS rate of 95.5% at 5 years (Figure 1).

Outcome of regional nodal metastasis

Five cases with regional nodal metastasis treated by tri-modality with whole pelvis EBRT showed neither biochemical failure nor clinical failure. A representative case with regional nodal metastasis treated in the present study is shown in Figure 2.

Toxicity

Acute grade 2 gastrointestinal (GI) and genitourinary (GU) toxicity was experienced by two patients (1.3%) and 15 patients (10.4%), respectively. Late grade 2 gastroin-

Table 3. Dosimetric parameters of seeds implantation and total biologically effective dose (BED)

Variables	Median (range)
Prostate D_{90} (Gy)	133.1 (95.7-153.9)
V_{100} (%)	97.3 (82.1-99.8)
UD_{30} (Gy)	166.5 (126.2-231.9)
R_{100} (cc)	0.29 (0-2.0)
Total BED (Gy)	220.9 (185.5-236.4)

BED – biologically effective dose, D_{90} – minimal dose (Gy) received by 90% of the prostate, V_{100} – the percentage prostate volume receiving 100% of the prescribed minimal peripheral dose, UD_{30} – minimal dose (Gy) by 30% of the urethra, R_{100} – rectal volume (ml) receiving 100% of the prescribed dose

Table 4. Distribution of total biologically effective dose (BED)

Variables	Number of cases
190 > BED ≥ 185	1
195 > BED ≥ 190	1
200 > BED ≥ 195	5
205 > BED ≥ 200	5
210 > BED ≥ 205	3
215 > BED ≥ 210	9
220 > BED ≥ 215	13
BED ≥ 220	106

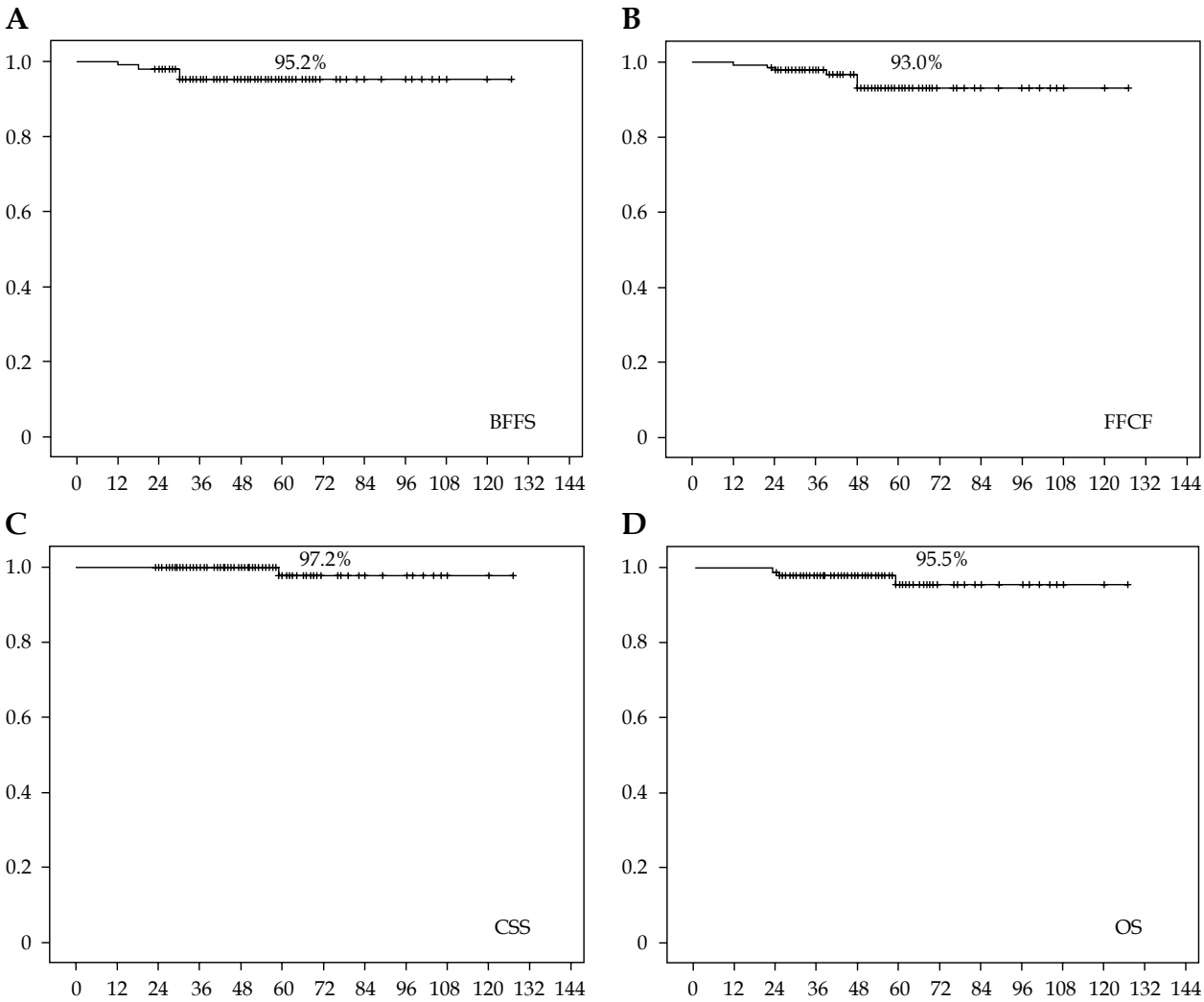

Fig. 1. Kaplan-Meier biochemical failure-free survival (BFFS), freedom from clinical failure (FFCF), cause-specific survival (CSS), and overall survival (OS). Y axis: survival probability; X axis: follow-up time after completion of external beam radiotherapy (EBRT) (months)

testinal (GI) and genitourinary (GU) toxicity was experienced by three patients (2.0%) and six patients (4.1%), respectively. One patient received preventive hyperbaric oxygen therapy for grade 2 rectal bleeding due to pancytopenia caused to end-stage renal malfunction. One patient received platelet transfusion for idiopathic platelet deficiency, although the patient did not have rectal bleeding. None of the patients experienced grade > 3 acute or late toxicity. None of the patients experienced urethral stricture, transurethral resection of prostate (TURP), or recto-urethral fistula.

Pattern of biochemical failure and number of high-risk features

Six out of the six patients (100%) with biochemical failure developed distant metastasis due to bone metastasis. Of those, 4 patients experienced one high-risk feature (6.7% of the cases with one risk), one patient had two high-risk features (1.6% of the cases with two risks), and one patient had three high-risk features (4.5% of the cases with three risks). Thus, the number of high-risk features did not have impact on disease recurrence. All the six patients showed a similar pattern of biochemical failure. A continuous PSA increase was observed after cessation of ADT. The median (range) time to biochemical failure was 23 (12-30) months with 100% failing within the first 3 years. The median (range) time from biochemical failure to distant metastasis was 9 (0-18) months.

Discussion

The present data have shown an excellent clinical outcome by high-dose (BED > 220 Gy) radiotherapy using LDR in combination with EBRT and ADT. The BED in the present study is the highest compared with those in the previous studies using LDR brachytherapy [10,11].

To achieve a BED of 220 Gy, D_{90} of 130 Gy had to be delivered (post-implant D_{90}) by using ^{125}I seed implantation in combination with the 45 Gy of EBRT in 1.8 Gy fraction. Several groups have demonstrated effectiveness of LDR in combination with EBRT and ADT for high-

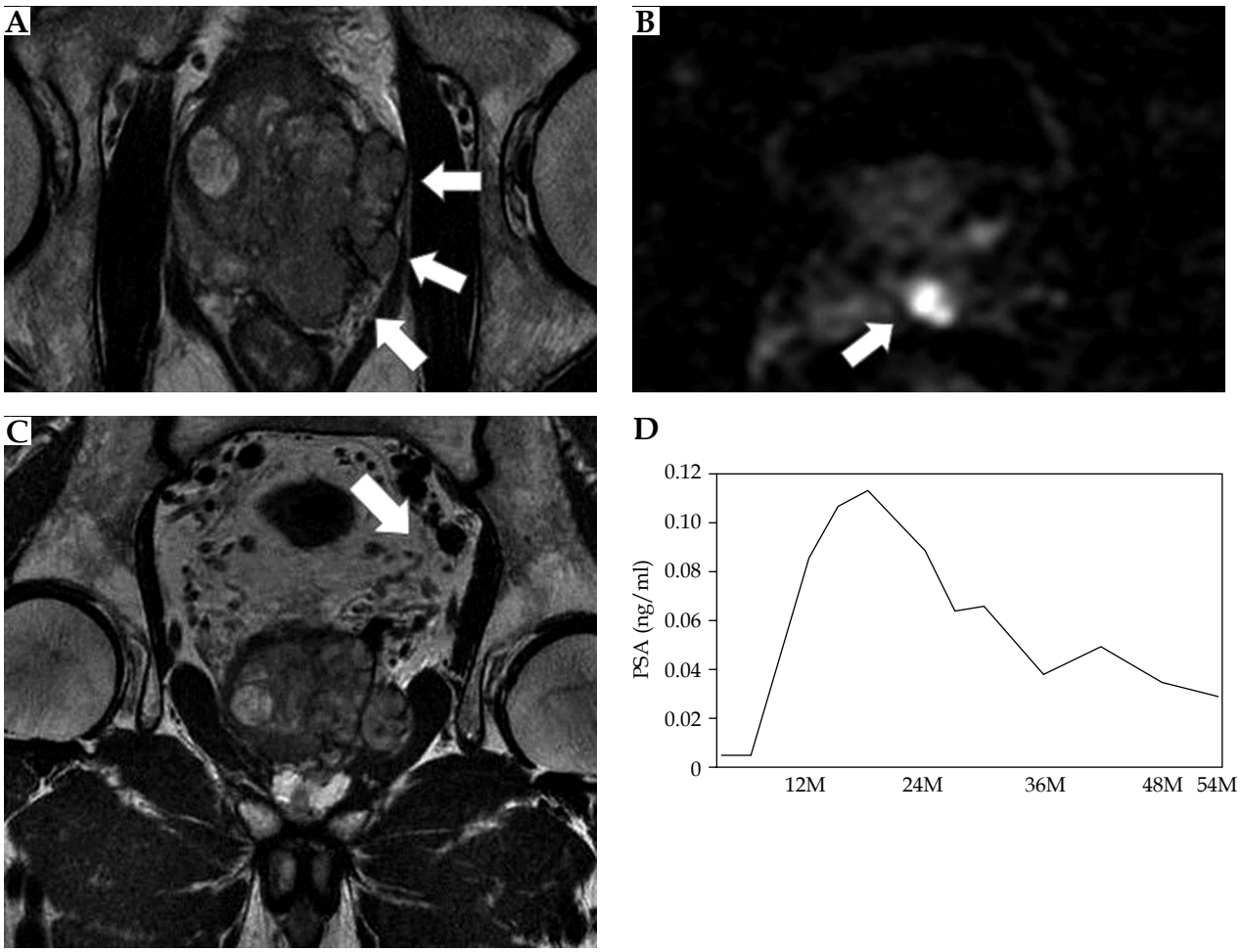

Fig. 2. Representative T3bN1 case treated by tri-modality with whole pelvis external beam radiotherapy (EBRT). Case: 68-year-old man with initial prostate-specific antigen (PSA) 65 ng/ml. The needle biopsy Gleason's score was 4+4. Clinical stage was T3bN1. Magnetic resonance imaging shows **(A)** a bulky prostate tumor extending over the capsule and compressing the rectal wall **(B)** with seminal vesicle invasion, and **(C)** nodal metastasis as indicated by white arrows. The patient was treated by combination therapy with low-dose-rate (LDR) brachytherapy, whole pelvis EBRT, and androgen deprivation therapy (ADT). Upon seeds implantation, they were implanted in seminal vesicle as well as prostate [15]; **(D)** PSA change after treatment: PSA shows temporal increase after cessation of ADT, but continuous decrease was observed thereafter. Y axis shows the period (months) from completion of the EBRT

risk prostate cancer [10,11]. They have shown favorable biochemical relapse-free rates at 5 years of 79% [10] and 84.8% [11]. In terms of profiles of high-risk prostate cancer patients, it should be noted that this study consists of a significant number of very high-risk prostate cancer patients with two high-risk factors (43%) and three high-risk factors (15%), including 5 cases (3%) with N1 disease and 21 cases (15%) with T3b or T4 disease. Furthermore, the initial PSA was higher than that of the previous studies using LDR in combination with EBRT for high-risk prostate cancer [10,11].

The present data have shown a 5 year BFFS at 95.2%. Similarly, high-dose-rate (HDR) brachytherapy is a modality that can deliver high BED in combination with EBRT. A previous study using HDR-based radiotherapy in combination with EBRT and long-term ADT, demonstrated a favorable 5 year BFFS of 85.1% with a median follow-up of 44 months for high-risk and very high-risk prostate cancer patients, including some in the intermediate risk category [12]. The data showed that biochemical failure occurred at a median of 40 months [12].

Kamrava *et al*. also reported on HDR based radiotherapy in combination with EBRT; they observed biochemical relapse in 14% of high-risk prostate cancer with a median failure time of 45 months [13]. However, a strict comparison with other reports on different treatment modalities is difficult because of the limitation and heterogeneity of each study. The present study has shown that biochemical failure occurred exclusively in cases with distant metastasis. This observation should be confirmed through a longer follow-up because local failure could occur later [14,15].

Biochemical failure and clinical failure were observed independent of the number of high-risk features. As Stone *et al*. suggested, the optimal BED for high-grade prostate cancer with a Gleason score of 8-10 is 220 Gy by multicenter

analysis [7]. The group also demonstrated that in a subset of biopsy-proven T3a, T3b, or N1 disease, the 7 year BFFS is 60% and 74% for BED below 200 Gy, and 200 Gy or above, respectively [10]. The present data has shown by a single institutional study that patients with high-risk and very high-risk prostate cancer, including N1 disease, show excellent biochemical control by receiving BED > 220 Gy.

Toxicity in the present study is minimal when compared with the previous reports using LDR [3,11] and HDR [12,13,14] in combination with EBRT. Although the total number of N1 disease patients in the present study was limited, the good biochemical control obtained using LDR in combination with whole pelvis EBRT is encouraging. Small nodal metastases may be well controlled with 45 Gy EBRT plus short-term ADT if the local prostate receives a high radiation dose (BED > 220 Gy), although much longer follow-up is required.

Our study limitations included: 1) short period of follow-up; 2) retrospective character of this study; 3) seminal vesicle and nodal involvement was diagnosed not by biopsy-proven, but by radiologic findings only. Even considering the above-mentioned shortcomings, this study has suggested that high-dose (BED > 220 Gy) radiotherapy by LDR in combination with EBRT may have an impact on BFFS in high-risk and very high-risk cancer.

Although a longer follow-up is necessary to validate the present findings, the reproducibility of this approach should be verified in order to use it as one of the optimal treatment modalities for high-risk and very high-risk prostate cancer patients.

Conclusions

High-dose (BED > 220 Gy) radiotherapy by LDR in combination with EBRT has shown an excellent outcome on BFFS in high-risk and very high-risk cancer patients, although causal relationship between BED and BFFS remain to be elucidated further.

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