A retrospective study of late adverse events in proton beam therapy for prostate cancer

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Abstract. The efficacy and safety of proton beam therapy (PBT) were retrospectively evaluated in 111 consecutive patients with prostate cancer who underwent definitive PBT between 2008 and 2012. Following exclusion of 18 patients due to treatment suspension, loss to follow-up, and histology, the analysis included 93 patients with a median age of 68 years (range, 49-81 years). A total of 7, 32 and 54 prostate cancer patients were classified as low-, intermediate- and high-risk, respectively, as follows: High-risk, T≥3a or prostate-specific antigen (PSA) ≥20 ng/ml or Gleason Score ≥8; low-risk, T ≤2b and PSA≤10 ng/ml and Gleason Score=6; intermediate-risk, all other combinations. The median initial prostate-specific antigen (PSA) level was 9.75 ng/ml (range, 1.4-100 ng/ml) and the median Gleason score was 7 (range, 6-10). Patients with low-risk disease received 74 GyE (relative biological effectiveness=1.1) in 37 fractions, and those at intermediate or higher risk received 78 GyE in 39 fractions. Complete androgen blockade (CAB) therapy was performed from 6 months prior to PBT for patients with intermediate- or high-risk disease. CAB was continued during PBT and then terminated at the end of PBT for intermediate-risk patients. Patients at high risk continued CAB for 3 years. No combination therapy was used for low-risk patients. All the patients were followed up for >2 years after PBT, and all but one were PSA failure-free. The Common Terminology Criteria for Adverse Events v.4.0 was used to evaluate late adverse events. One patient developed grade 3 non-infectious cystitis and hematuria. Grade 2 urinary frequency was observed in 1 patient, and grade 2 rectal bleeding occurred in 4 patients. Of the 4 patients with grade 2 rectal bleeding, 2 received anticoagulant therapy, but none had diabetes mellitus or another high-risk comorbidity. The median time to occurrence of an adverse event of grade ≥2 was 14 months (range, 3-41 months). Therefore, the present retrospective study revealed that PBT at 78 GyE/39 Fr was well-tolerated and achieved good tumor control in patients with prostate cancer.

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Introduction

Radiation therapy is standard treatment for localized prostate cancer, but late adverse events, such as rectal bleeding, are a major concern, with a reported risk of 5-20% for genitourinary (GU) and gastrointestinal (GI) adverse events of grade ≥2 (1,2). The irradiated dose and volume to an organ at risk (OAR) are correlated with the frequency of late adverse events (1,3), but higher local doses also achieve better local control (4,5). Thus, a high radiation dose to the target and reduction of OAR doses are critical factors in radiation therapy. The emergence of image-guided radiotherapy (IGRT), 3-dimentional conformal radiotherapy (3D-CRT), and its successor, intensity-modulated radiotherapy (IMRT), has significantly lowered toxicity to the bladder and rectum, although 5-10% of the patients develop grade 2 or more severe toxicity (5-7).

Charged particle beams, such as those used in proton beam therapy (PBT), deliver high radiation doses to the target in a conformal manner, which minimizes the doses to OARs. These advantages are based on the fundamental physical dose distribution of charged particle beams (8). However, the number of clinical trials on PBT for prostate cancer is limited. A dose escalation study using PBT as a boost yielded favorable results (9), but with limited follow-up of patients who received PBT alone. We herein report a retrospective review of the efficacy and safety of PBT for prostate cancer.

Patients and methods

Patients. A total of 111 consecutive patients underwent definitive PBT for prostate cancer at the Department of Radiation Oncology and Proton Medical Research Center (Tsukuba, Japan) between 2008 and 2012. A total of 11 patients were excluded due to incomplete treatment, 6 were lost to follow-up, and 1 had a different histological type of tumor, namely basal cell carcinoma. Therefore, a total of 93 patients were analyzed in the present study. The patient characteristics are summarized in Table I. Staging evaluation was performed by digital rectal examination, MRI, CT and bone scintigraphy.

Risk stratification. In risk classification of prostate cancer (Table II), patients with all low-risk factors were classified as low-risk; those with any high-risk factor as high-risk; and those with any other combination as intermediate-risk. Complete androgen blockade (CAB) was performed from 6 months prior to PBT for intermediate- or high-risk cases, and patients at high risk continued CAB for 3 years. No combination therapy was used for low-risk cases based on our criteria.

Radiotherapy systems. The PBT system consisted of a 250 MeV synchrotron equipped with an isocentric rotational gantry, a 15x15-cm passive scattering port with a 5-mm multileaf collimator, a rotational treatment couch, and a treatment-planning system (Hitachi 3D Treatment Planning System ver. 2.0; Hitachi Ltd., Tokyo, Japan) with a CT scanner and an X-ray simulator without any modifications. Dose volume histogram (DVH) parameters were calculated using the same treatment-planning system.

Principles of treatment planning. Target volume and risk organs were defined as follows: The clinical target volume (CTV) was set as the prostate plus 1/3 caudal seminal vesicle (whole seminal vesicle for cT3b). The planning target volume (PTV) was defined as the CTV plus a 10-mm lateral, 12-mm anterior, and 5-mm craniocaudal and posterior margins. The rectum was contoured from the sigmoid flexure to the anus or ischial tuberosity, whichever was closer to the PTV. Low-risk cases received 74 GyE (relative biological effectiveness=1.1) in 37 fractions, and intermediate- or high-risk cases received 78 GyE in 39 fractions. To reduce the dose to the rectum, the posterior edge of the PTV was set in front of the anterior wall of the rectum by using multileaf collimators after 30 fractions. Two lateral ports (one from either side) were used for treatment. Dose constraints to the rectum were set to the following: V50 <30%, V80 <20% and V90 <10%, although exceptions were permitted when the risk/benefit ratio was considered clinically acceptable. Dose constraints to the bladder were not set, since this was not an issue due to the beam angle set-up.

Patient preparation and fixation. Prior to treatment planning, the patients had fiducial markers installed in their prostate by a transrectal method for positioning verification. Image-guided patient position verification was performed using orthogonal X-ray images for every fraction. In order to control bladder volume, the patients were asked to completely void their bladders 30 min prior to treatment and to drink one cup (~100 ml) of tea. Bladder volume was confirmed to be ~100 ml, immediately prior to treatment using ultrasonic bladder volume measuring instruments. Fixation was performed using foot and leg rests without thermal plastic shells.

Follow-up. Regular follow-up included physical examinations and prostate-specific antigen (PSA) blood tests at 3- to 4-month intervals for the first 2 years and at 3- to 6-month intervals thereafter. Treatment-related morbidities were evaluated by physical examination and imaging. Events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Effects, version 4 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

Statistical analysis. Statistical analysis was performed using R software (http://www.r-project.org/). Gray analysis with death as a competing risk consideration was used for biochemical relapse-free rate and cumulative toxicity event rate calculations. Fine-Gray analysis was used for uni- and multivariate analysis. A P-value of <0.05 was considered to indicate statistically significant differences.

Results

Follow-up and outcome. The median follow-up time was 55 months (range, 32-97 months). All patients apart from one were PSA failure-free and the 5-year cumulative biochemical relapse-free rate was 99.0% (95% CI: 93.2-99.9%). Only one death was reported, which was due to pancreatic cancer. As regards late GU morbidity, grade 3 non-infectious cystitis occurred in 1 patient (1.5%) and grade 2 urinary frequency and hematuria were observed in 4 (4.3%) and 1 (1.5%) patients, respectively. As regards late GI morbidity, grade 2 rectal bleeding was observed in 4 patients (4.3%). No other grade ≥2 adverse events were observed. The 5-year cumulative incidence of grade ≥2 GU and GI morbidities was 5.8 and 4.3%, respectively (Fig. 2). The median maximum dose to the PTV was 101.5% [±0.21% two standard deviations (2SD)] of the prescribed dose. The median rectal V30 to V80 in 10% increments were 32.5% (±16.2% 2SD), 28.0% (±17.9%), 23.8% (±13.4%), 20.0% (±11.9%), 16.5% (±10.4%) and 12.5% (±8.6%), respectively. The rectal doses in patients with and without grade 2 GI toxicity are shown in Table III. All doses were higher in patients with grade 2 GI toxicity, but the difference was not statistically significant. On multivariate analysis, the use of anticoagulants was a significant positive risk factor [hazard ratio (HR)=5.72, 95% confidence interval (CI): 1.31-24.92] and the PTV volume was a significant negative risk factor (HR=0.96, 95% CI: 0.937-0.983) for grade 2 rectal bleeding. Age, Gleason score, initial PSA, prescription dose, and T3b disease were not found to be significant.

Discussion

Late toxicity following radiotherapy for prostate cancer has been a major concern from the start of use of this therapy (10). The emergence of 3D-CRT demonstrated that a high radiation dose to the target leads to better biochemical disease-free survival (4,5,11), but is also associated with higher toxicity (4,5). Several studies have investigated risk factors associated with late toxicities following radiotherapy for prostate cancer, and the irradiation dose and volume to the rectum and use of anticoagulants are considered to be key factors (1,3,12,13).

The use of IGRT is also known to improve the actual dose to the rectum and, therefore, improve clinical results (14). A significant decrease in rectal toxicity was observed with the use of IGRT for high-dose irradiation (15).

Table I. Patient characteristics.

Characteristics	No. (%)
Age, years	
Median (range)	68 (49-81)
T stage	
T1c	24 (26)
T2a-T2b	30 (32)
T2c	11 (12)
T3a	20 (22)
T3b	7 (8)
T4	1 (1)
Initial PSA value (ng/ml)	
<10.0	47 (51)
10.0-19.9	21 (23)
≥20.0	25 (27)
Gleason score sum	
≤6	14 (15)
7	33 (35)
≥8	46 (49)
Tumor risk group	
High	54 (49)
Intermediate	32 (35)
Low	7 (8)
Antithrombotic drugs	
Yes	10 (11)
No	83 (89)

PSA, prostate-specific antigen.

Table II. Risk classification for treatment in our institution.

Factors	Low-risk	High-risk
T stage	T1c-2b	T3a-b, T4
iPSA (ng/ml)	<10.0	≥20.0
Gleason score sum	≤6	≥8

Low-risk, all low-risk factors; high-risk, any high-risk factor; intermediate-risk, any other combination. iPSA, initial prostate-specific antigen.

Charged particle beams, such as those used in PBT, deliver high radiation doses to the target in a conformal manner, which minimizes the doses to OARs. This is realized by the unique fundamental physical characteristics known as Bragg peak, and by modulating it with the use of spread-out Bragg peak and collimators (8,16). Alongside adequate re-planning, as described earlier, our rectal doses where lower compared with all parameters in other 3D-CRT studies (1,17). Also, compared with IMRT studies, the high doses were comparable, and the intermediate doses were lower (18). Bladder doses have not been evaluated in detail; however, since we only utilized lateral irradiation ports (2 ports, Fig. 1), a low to intermediate dose to the bladder was sufficiently low.

Table III. Dose volume histogram comparison with and without late toxicity.

	Grade <2		Grade 2		
Dosimetry	%	2SD	%	2SD	P-value
V30	33.6	±16.3	37.3	±13.6	0.37
V40	28.9	±15.0	32.2	±12.0	0.387
V50	24.8	±13.6	27.9	±10.0	0.365
V60	20.8	±12.1	23.4	±8.0	0.394
V70	16.9	±10.5	19.3	±6.1	0.365
V80	12.5	±7.7	14.0	±4.6	0.497

2SD, two standard deviations.

As regards clinical results, with the use of fiducial markers and daily IGRT, grade 2 rectal bleeding developed in 4 patients (4.3%), grade ≥2 hematuria was observed in 2 patients (2.1%) and grade 2 urinary frequency occurred in 4 patients (4.3%). No other grade ≥2 late adverse events were observed. Rectal toxicity was comparable with that of IMRT and lower compared with that of 3D-CRT, and genitourinary toxicity was better compared with that of both 3D-CRT and IMRT (Table IV) (7,19-30).

Unfortunately, due to the low toxicity incidence rate, the availability of statistical analysis data on risk factors of GI toxicity is limited. Patients with grade 2 GI toxicity had higher V30 to V80 rectal doses, but the difference was not significant. On multivariate analysis, the use of anticoagulants was the only significant positive risk factor, and PTV volume was a negative risk factor. Age, Gleason score, initial PSA, prescription dose and T3b disease were not significant factors, and these findings did not change after excluding PTV volume in the analysis. DVH analysis revealed higher doses, although without a significant difference, in patients with grade 2 GI toxicity, which is consistent with previous studies reporting rectal dose as a risk factor (1,3). The DVH parameters likely failed to be significant due to the low event rate, with only 4 patients suffering grade 2 rectal bleeding, including 2 who received anticoagulant therapy. A larger PTV volume was not found to be a risk factor for GI toxicity, in contrast to findings supporting that a large PTV volume is a positive risk factor in other modalities (31). In addition to the low grade 2 incidence rate, this may be explained by our irradiation method. The PTV volume is enlarged by prostate hypertrophy and T3b disease, thus affecting the rectal dose. PBT is known to deliver a lower dose to the rectum and bladder, particularly in high-risk cases where seminal vesicle irradiation is required (32,33), which supports the results of the present study.

GU toxicity was relatively low compared with that in previous reports. We consider this to be due to the conformal dose distribution in passive PBT. Heterogeneity of the radiation dose within the target is reported to predispose patients to urethral strictures (34). The maximum dose in the present study was 101.5% (±0.21% 2SD) of the prescribed dose, which is a difficult value to achieve using IMRT or scanning

Table IV. List of previous reports on the results of treatment for prostate cancer.

				5-year BFS (%)			Grade ≥2 toxicity[a]		
First author	Method	Dose (Gy)	Gy/Fr	Low	Intermediate	High	GI	GU	(Refs.)
D'Amico	3D-CRT	66-70	2	80	65-75	40	N/A	N/A	(19)
Dearnaley	3D-CRT	74	2	85	79	57	43	15	(20)
Vora	3D-CRT	66-71	1.8-2	76	50	35	16	22	(21)
Zepatero	3D-CRT	76-82	2	N/A	88	88	10.1	9.9	(7)
Zelefsky	IMRT	81	1.8	85	76	72	1.8	12.2	(22)
Kupelian	IMRT	70	2.5	94	83	72	1.8	12.2	(23)
Vora	IMRT	70.2-77.4	1.8	88	70	60	24	29	(21)
Cahlon	IMRT	70	2.5	94	83	72	6	7	(24)
Martin	IMRT	79.8	1.77	88	77	78	13.7	12.1	(25)
Guckeznberger	IMRT	73.9-76.2	2.3	88	80	78	4.8	22.4	(26)
Schulte	PBT	74-75	1.8-2		82		3.5	5.4	(27)
Mendenhall	PBT	78-82	2	99	99	76	1.0	0.9	(28)
Takagi	PBT	74	2	99	91	86	3.8	1.9	(29)
Bryant	PBT	72-82	2	94	88	88	N/A	N/A	(30)
Present study	PBT	74-78	2		99		5.4	1.0	

[a]Late toxicity only. BFS, biochemical relapse-free survival rate; GI, gastrointestinal; GU, genitourinary; PBT, proton beam therapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; N/A, not available.

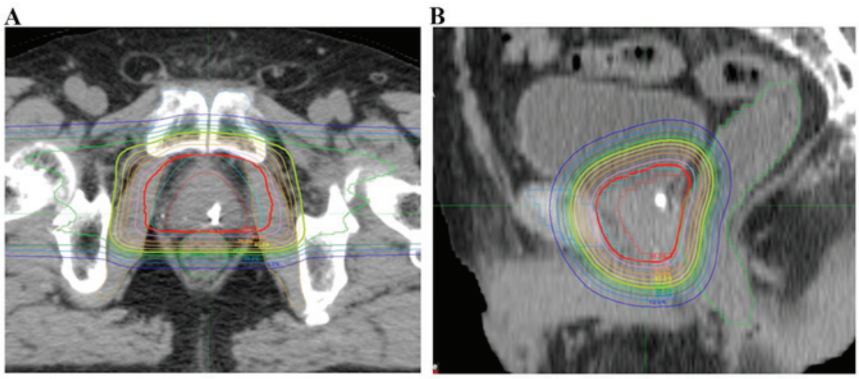

Figure 1. Typical dose distribution for the treatment of prostate cancer using proton beam therapy: (A) Axial and (B) sagittal view.

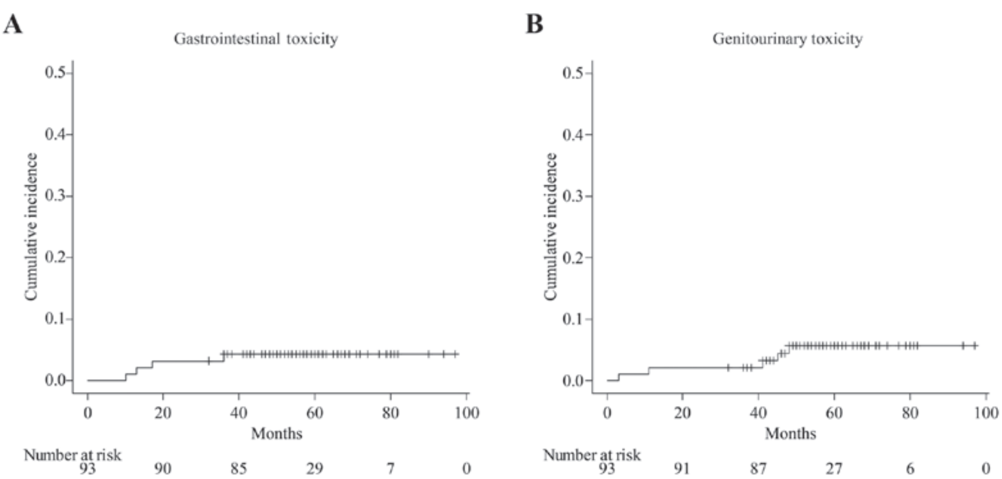

Figure 2. Cumulative (A) gastrointestinal and (B) genitourinary adverse events of grade ≥2.

PBT (35). This conformal dose may be an explanation for the low GU toxicity. Also, as discussed above, only lateral beams were used in PBT for prostate cancer, thus lowering the low to intermediate doses to the bladder.

Various approaches have been assessed to decrease late toxicity in prostate cancer treatment. Hypofractionation is considered to decrease the biological effective dose to the rectum due to the nature of prostate cancer, although extreme hypofractionation may result in compromising tumor control due to the heterogeneity of cancer (36). The use of carbon-ion radiotherapy is a more straightforward method for improving dose distribution with promising results, although it requires specialized equipment and a vast amount of space (3,37).

The biological effectiveness of PBT is considered to be slightly higher compared with that of high-voltage X-ray/cobalt-60, raising the relative biological effectiveness to 1.1 (38). This 10% change in biological effectiveness may contribute to better tumor control, but it is unclear without a randomized control study to evaluate such detailed difference. In the present study, all patients but one were PSA failure-free and the 5-year cumulative biochemical relapse-free rate was 99.0%. Considering that the follow-up period was relatively short, with a median follow-up of just under 5 years, it is difficult to suggest better tumor control compared with other treatments, but the results appear to be promising. In addition, all the patients were observed for >48 months, which is sufficient for toxicity analysis, and the observed toxicities were minimal. We consider these results as promising, and PBT may be considered as a treatment option for prostate cancer. To elucidate the advantage of PBT over X-ray therapy, multiple prospective multi-center single-arm trials are currently underway.

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