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Original Article

Prostate-specific antigen kinetics following hypofractionated stereotactic body radiotherapy boost as post-external beam radiotherapy versus conventionally fractionated external beam radiotherapy for localized prostate cancer

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ABSTRACT

Background: Stereotactic body radiotherapy (SBRT) has emerged as an effective treatment for localized prostate cancer. The purpose of this study was to compare the prostate-specific antigen (PSA) kinetics between conventionally fractionated external beam radiotherapy (CF-EBRT) and SBRT boost after whole pelvis EBRT (WP-EBRT) in localized prostate cancer.

Methods: A total of 77 patients with localized prostate cancer [T-stage, T1–T3; Gleason score (GS) 5–9; PSA < 20 ng/mL] were enrolled. A total of 35 patients were treated with SBRT boost (21 Gy in 3 fractions) after WP-EBRT and 42 patients were treated with CF-EBRT (45 Gy WP-EBRT and boost of 25.2–30.6 Gy in 1.8-Gy fractions). PSA nadir and rate of change in PSA (slope) were calculated and compared.

Results: With a median follow-up of 52.4 months (range, 14–74 months), the median PSA nadir and slope for SBRT boost were 0.29 ng/mL and −0.506, −0.235, −0.129, and −0.092 ng/mL/mo, respectively, for durations of 1 year, 2 years, 3 years, and 4 years postradiotherapy. Similarly, for CF-EBRT, the median PSA nadir and slopes were 0.39 ng/mL and −0.720 ng/mL/mo, −0.204 ng/mL/mo, −0.121 ng/mL/mo, and −0.067 ng/mL/mo, respectively. The slope of CF-EBRT was significantly different with a greater median rate of change for 1 year postradiotherapy than that of SBRT boost ($P = 0.018$). Contrastively, the slopes of SBRT boost for durations of 2 years, 3 years, and 4 years tended to be continuously greater than that of CF-EBRT. The significantly lower PSA nadir was observed in SBRT boost (median nadir 0.29 ng/mL) compared with CF-EBRT (median nadir 0.35 ng/mL, $P = 0.025$). Five-year biochemical failure (BCF) free survival was 94.3% for SBRT boost and 78.6% for CF-EBRT ($P = 0.012$).

Conclusion: Patients treated with SBRT boost after WP-EBRT experienced a lower PSA nadir and there tended to be a continuously greater rate of decline of PSA for durations of 2 years, 3 years, and 4 years than with CF-EBRT. The improved PSA kinetics of SBRT boost over CF-EBRT led to favorable BCF free survival.

1. Introduction

Prostate cancer is the most common cancer and the second leading cause of death among men in the United States[1] and the incidence rates in Korea are relatively lower than those in western nations. However, they continue to increase annually owing to the aging of society, adoption of westernized lifestyle, and addition of the prostate-specific antigen (PSA) screening test to the National Cancer Screening Program.[2] As the prevalence of prostate cancer increases, various treatment modalities are considered. External beam radiotherapy (EBRT) is a conventional treatment option for localized prostate cancer.[3]

Accumulating recent clinical evidence has demonstrated that that the α/β ratio of prostate cancer is around 2 Gy and lower than that of the surrounding normal tissue.[4,5] The hypofractionated radiotherapy schema may improve the biochemical control of prostate cancer without increasing toxicities associated with late-

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responding tissue.[4] Recently, hypofractionated stereotactic body radiotherapy (SBRT) boost after EBRT has demonstrated excellent efficacy and toxicity profiles.[6,7]

The PSA test is the most common initial test for men who are worried about prostate cancer.[8] However, PSA is a well-established biomarker for prostate cancer and available for monitoring response to treatment. In patients without androgen deprivation therapy (ADT), analysis of PSA kinetics after treatment could reveal the biologic effect of radiation on prostate cancer. The changes of PSA after radical prostatectomy, EBRT, and brachytherapy have been extensively researched.[9] Lower PSA nadir and rapid decline in PSA after treatment have been related to improved clinical outcome.[10–13] While recent studies have demonstrated that a lower PSA nadir (< 0.5 ng/mL) has been associated with superior clinical disease free survival,[13,14] the interpretation of the decline rate of PSA following radiotherapy is controversial. Some reports have shown a positive relationship between the increase of the decline rate and clinical outcome, while others have been negative.[15–19] Furthermore, kinetics of PSA decline following SBRT using Cyberknife remains poorly understood and there are only a few reports from western countries.[20,21] It is necessary to elucidate the kinetics of SBRT in Asian populations. The objective of this study is to compare the PSA kinetics (nadir and rate of decline of PSA) of hypofractionated SBRT boost after whole pelvis EBRT (WP-EBRT) with conventionally fractionated EBRT (CF-EBRT) in localized prostate cancer.

2. Materials and methods

2.1. Patient characteristics

From 2008 to 2014, 35 patients newly diagnosed with localized prostate cancer who were treated with SBRT boost after WP-EBRT using the Cyberknife robotic radiosurgery system (Accurray Incorporated, Sunnyvale, CA, USA) were enrolled in this retrospective analysis. All patients had histologically confirmed primary adenocarcinoma of the prostate. None of these patients had received any other local or systemic primary treatment of prostate cancer. Prior transurethral resection of the prostate for urinary symptom relief was allowed. Patients were stratified according to 2.2014 NCCN risk stratification guidelines.[22] The study was approved by the Ethical Committee for Clinical Trials of our institution and the retrospective data was prospectively collected in our institutional database. In order to have a homogenous initial PSA level in this group, we excluded patients whose initial PSA level was above 20 ng/mL in high-risk prostate cancer patients. In order to assess PSA kinetics in response to radiotherapy alone, we stopped follow-up on the PSA evaluation if they failed therapy by Phoenix definition.[23] PSA values taken after the start of ADT were excluded. All included patients had at least 1 year of follow-up. PSA bounce was defined as an absolute increase of 0.2 ng/mL from the previous PSA level, followed by a subsequent decrease.[24] Toxicity was documented at follow-up visits using the Radiation Therapy Oncology Groups scale. To compare the cohort of patients treated with CF-EBRT, the records from a prospectively collected cohort of patients treated at our institute from 2006 through 2012 were reviewed. We identified 42 patients treated with CF-EBRT who met the above inclusion criteria. All patients treated with CF-EBRT alone received doses between 70.2 Gy and 75.6 Gy. A comparison between the two radiotherapy cohorts of patient baseline characteristics is shown in Table 1.

Table 1
Patient characteristics ($n = 77$).

Variables	SBRT boost ($n = 35$)	CF-EBRT ($n = 42$)	*P*
Mean age (range)	69.4 (60–78)	71.1 (61–79)	0.212
ECOG scale			0.566
0	22 (62.9%)	28 (66.7%)	
1	12 (37.1%)	14 (33.3%)	
T stage			0.257
T1–T2a	2 (5.7%)	7 (16.7%)	
T2b–T2c	29 (82.9%)	34 (80.9%)	
T3a	4 (11.4%)	1 (2.4%)	
GS			0.087
≤ 6	6 (17.2%)	15 (35.7%)	
7	25 (71.4%)	19 (45.2%)	
≥ 8	4 (11.4%)	8 (19.1%)	
Pretreatment PSA (ng/mL)			
Mean (range)	9.06 (4.46–19.50)	10.64 (5.34–18.70)	0.711
< 10	26 (74.3%)	23 (54.8%)	
≥ 10	9 (25.7%)	19 (45.2%)	
NCCN risk group			0.705
Low	0 (0%)	6 (14.3%)	
Intermediate	31 (88.6%)	29 (69.0%)	
High	4 (11.4%)	7 (16.7%)	

CF-EBRT, conventionally fractionated external beam radiotherapy; ECOG scale, Eastern Cooperative Oncology Group performance scale; GS, Gleason score; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; SBRT, stereotactic body radiotherapy.

2.2. Whole pelvis radiotherapy and SBRT boost treatment planning and delivery

Four or more gold fiducial markers were implanted transperineally into the prostate. After 7 days, patients underwent MR imaging and thin-cut CT scan. Fused CT and MR images were used for the treatment planning. The prostate, seminal vesicles, rectum, bladder, penile bulb, and bowel were contoured. The prostate gland, the seminal vesicles, and the area of radiographic extracapsular extension were defined as the clinical target volume (CTV1). CTV2 included the external iliac nodes, the internal iliac nodes, the presacral nodes, and the obturator nodes. The planning target volume (PTV1) was extended 7 mm beyond the CTV1 in all directions, except in the posterior direction, wherein it was extended 5 mm. The PTV2 was extended 7 mm in all directions. The prescription dose of WPRT was 45 Gy and was administered in 25 fractions. A minimum of 95% of the prescription dose was assured to cover 100% of the PTV. All WPRT treatment plans were generated on Varian Eclipse treatment planning system (version 8.8.6, Varian Medical Systems, Palo Alto, CA, USA).

In SBRT boost planning, the prostate gland, the seminal vesicles, and the area of radiographic extracapsular extension were defined as the CTV which was the same as that of the WPRT treatment plans. The PTV extended 5 mm beyond the CTV in all directions, except in the posterior direction, wherein it was extended 3 mm. The prescription boost dose of 21 Gy, delivered in three fractions, was prescribed to the PTV. The prescription dose covered at least 95% of the PTV, normalized to the 75–85% isodose line [mean homogeneity index of 1.31 (range, 1.21–1.41)]. The rectal dose-volume goals were < 50% of the rectal volume receiving 50% of the prescribed dose, < 20% receiving 80% of the dose, < 10% receiving 90% dose, and < 5% receiving 100% of the dose. Treatments were given over 3 consecutive days.

2.3. CF-EBRT treatment planning and delivery

The CTV included the prostate, seminal vesicles, and internal iliac, external iliac, and obturator nodal regions. The upper limit of the CTV was the level of the common iliac bifurcation, which was

generally located at or just above the L5/S1 junction. The PTV was a 5–7 mm expansion of the CTV. The prescription dose of WPRT was 45 Gy and was administered in 25 fractions. A minimum of 95% of the prescription dose was assured to cover 100% of the PTV. After pelvic radiotherapy, the boost treatment included only the prostate and seminal vesicles. The boost dose of 25.2–30.6 Gy in 1.8-Gy fractions was administered. All CF-EBRT treatment plans were generated on Varian Eclipse treatment planning system (version 8.8.6, Varian Medical Systems).

2.4. Statistical analysis

To eliminate the effect of differing follow-up durations between SBRT boost after EBRT and CF-EBRT, we calculated the rate of change in PSA over an interval of time from the completion of radiotherapy to 1 year, 2 years, 3 years, and 4 years posttreatment. The slope of PSA change (ng/mL/mo) was calculated as the regression coefficient in a linear regression model for each individual.[25] The *t* test was performed to compare mean values and analysis of variance in continuous variables and the Mann–Whitney test was used to compare distributions of the slope of PSA. Biochemical failure (BCF) free survival was estimated using the Kaplan–Meier method. Statistical analysis was performed using the IBM SPSS software, version 19.0 (SPSS, Inc., IBM, Chicago, IL, USA).

3. Results

All patients completed the treatment. Seventy-seven patients with a median of 52.4 months (range, 14–74 mo) follow-up were analyzed. The pretreatment median PSA levels were 9.06 ng/mL (4.46–19.50 ng/mL) in SBRT boost and 10.64 ng/mL (5.34–18.70 ng/mL) in CF-EBRT ($P = 4.46–19.50$; $P = 0.711$, Table 1).

Fig. 1 shows PSA changes declining over times, with different rates of PSA decline for each time interval since radiotherapy. To investigate the PSA kinetics after radiotherapy, the rate of PSA decline (slope) was calculated for four intervals following radiotherapy (0–1 year, 0–2 years, 0–3 years, and 0–4 years). The rate of PSA decline (slope) for the CF-EBRT cohort was maximal in the 1st year, but tapered off in the following years, with median values of −0.720 ng/mL/mo, −0.204 ng/mL/mo, −0.121 ng/mL/mo, and −0.067 ng/mL/mo for durations of 1 year, 2 years, 3 years, and 4 years postradiotherapy, respectively (Table 2). Similarly, the slope of PSA for the SBRT boost was maximal in the 1st year with median values of −0.506 ng/mL/mo, −0.235 ng/mL/mo, −0.129 ng/mL/mo, and −0.092 ng/mL/mo for durations of 1 year, 2 years, 3 years, and 4 years, respectively. Although the magnitude of the slopes for both SBRT boost and CF-EBRT decreased with time, the slope of CF-EBRT was significantly different with a greater median rate of change for 1 year postradiotherapy than that of SBRT boost (−0.720 ng/mL/mo for CF-EBRT versus −0.506 ng/mL/mo for SBRT boost, $P = 0.018$). Contrastively, the slopes of SBRT boost for durations of 2 years, 3 years, and 4 years tended to be continuously greater than that of CF-EBRT (−0.235 ng/mL/mo, −0.129 ng/mL/mo, and −0.092 ng/mL/mo, respectively, for SBRT boost versus −0.204 ng/mL/mo, −0.121 ng/mL/mo, and −0.067 ng/mL/mo for CF-EBRT), although there were no statistical significances. Because the inclusion criteria make this a relatively homogenous population, there were no significant differences in the comparison of the rate of PSA decline by the Gleason score (≤ 6 vs. 7) and pretreatment PSA (≤ 10 vs. > 10).

Table 2
Comparison of the rate of prostate-specific antigen (PSA) decline of stereotactic body radiotherapy (SBRT) boost and conventionally fractionated external beam radiotherapy (CF-EBRT).

Through year	SBRT boost	CF-EBRT	*P*
0–1	−0.506	−0.720	0.018
0–2	−0.235	−0.204	0.051
0–3	−0.129	−0.121	0.799
0–4	−0.092	−0.067	0.375

CF-EBRT, conventionally fractionated external beam radiotherapy; SBRT, stereotactic body radiotherapy.

The PSA response as defined by PSA nadir has been excellent. The entire cohort has achieved a median 0.35 ng/mL (range, 0.04–1.44 ng/mL). The SBRT boost cohort achieved a median PSA nadir of 0.29 ng/mL (range, 0.04–1.44 ng/mL) with a median follow-up of 32.3 months and the CF-EBRT cohort achieved a median PSA nadir of 0.39 ng/mL (range, 0.04–1.82 ng/mL) with a median follow-up of 25.2 months (Fig. 2 and Table 3). The significantly lower PSA nadir was observed in the SBRT boost cohort ($P = 0.025$) and the time to PSA nadir was statistically longer for SBRT boost when compared to CF-EBRT ($P = 0.043$). Benign PSA

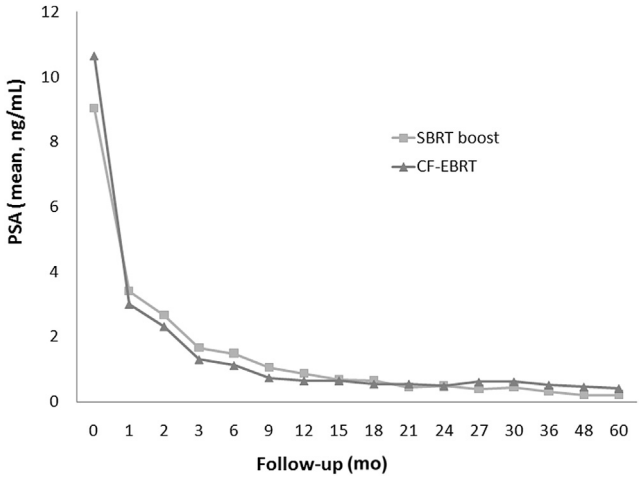

Fig. 1. Prostate-specific antigen changes after stereotactic body radiotherapy (SBRT) boost after external beam radiotherapy (EBRT) and conventionally fractionated EBRT (CF-EBRT).

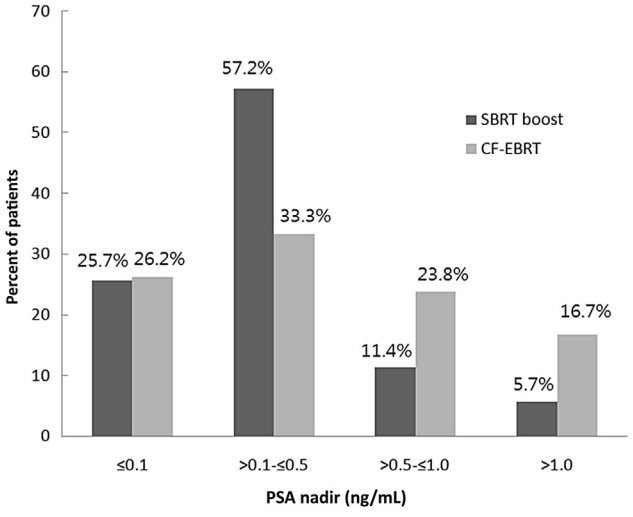

Fig. 2. The graph shows prostate-specific antigen (PSA) nadir after stereotactic body radiotherapy (SBRT) boost after external beam radiotherapy (EBRT) and conventionally fractionated EBRT (CF-EBRT).

Table 3
PSA kinetics of SBRT boost and CF-EBRT.

	SBRT boost	CF-EBRT	*P*
Median PSA nadir	0.29 ng/mL (0.04–1.44)	0.39 ng/mL (0.04–1.82)	0.025
PSA nadir ≤ 0.5 ng/mL	29 (82.9%)	25 (59.5%)	0.008
Median time to nadir	32.3 mo (12–51)	25.2 months (9–58)	0.043
PSA bounce	10 (28.6%)	9 (21.4%)	0.837
Median height of PSA bounce	0.28 ng/mL (0.21–0.58)	0.38 ng/mL (0.22–1.20)	0.222
Median time to bounce	11.6 mo (6–25)	16.0 mo (6–30)	0.388

CF-EBRT, conventionally fractionated external beam radiotherapy; PSA, prostate-specific antigen; SBRT, stereotactic body radiotherapy.

Table 4
Acute and late genitourinary and gastrointestinal toxicity of stereotactic body radiosurgery boost.

Variables		SBRT boost (%)	CF-EBRT (%)	*P*
Acute GU	Grade 1	48.6%	42.9%	0.852
	Grade 2	22.9%	38.1%	0.254
Acute GI	Grade 1	28.6%	40.4%	0.086
	Grade 2	20.0%	16.7%	0.586
Late GU	Grade 1	14.2%	11.9%	0.632
	Grade 2	8.6%	9.5%	0.256
Late GI	Grade 1	20.0%	14.3%	0.097
	Grade 2	11.4%	11.9%	0.152
	Grade 3	0.0%	2.3%	0.098

CF-EBRT, conventionally fractionated external beam radiotherapy; GI, gastrointestinal; GU, genitourinary; SBRT, stereotactic body radiotherapy.

bounces were common with 24.7% of all cohorts. The incidence of PSA bounce was more frequent in patients treated with SBRT boost compared to CF-EBRT (28.6% vs. 21.4%, $P = 0.837$), but there was no statistical significance. Patients with PSA bounces had lower pretreatment PSA levels (10.66 ng/mL vs. 7.68 ng/mL, $P = 0.014$) and were associated with a low-risk group ($P = 0.001$).

BCF were observed in two patients with SBRT boost and nine patients with CF-EBRT. The actuarial 5-year BCF free survival was 94.3% for patients treated with SBRT boost and 78.6% for CF-EBRT ($P = 0.012$, Fig. 3).

The frequency of toxicity events divided by treatment type is presented in Table 4. The prevalent acute toxicities after radiotherapy were urinary frequency and rectal pain but usually resolved within 1–2 months on basic symptomatic therapy. The difference in acute toxicity between SBRT boost and CF-EBRT was not statistically significant. The rates of late Grade 1–2 genitourinary (GU) and gastrointestinal (GI) toxicities were similar in both groups. There was only one Grade 3 late GI toxicity event in the CF-EBRT group. One patient in the CF-EBRT group complained of severe hematochezia and bowel habit change, which was surgically managed.

4. Discussion

In this report, we described the changes in the PSA levels in patients with localized prostate cancer treated with SBRT boost after WP-EBRT and CF-EBRT without ADT. The majority of PSA declines occurred in the 1st year but tapered off quickly in the following years at both treatment modalities. Several reports in PSA kinetics have shown that significant PSA change occurs in the 1st year following radiotherapy.[26,27] Consistently, in our study, the majority of the PSA decline occurred in the 1st year. Although the decline rate of PSA in CF-EBRT was greater through Year 1, the decline rate for SBRT boost did not fall off as quickly as CF-EBRT during 1 year, but declined consistently more rapidly for a duration of 2 years, 3 years, and 4 years than that of CF-EBRT.

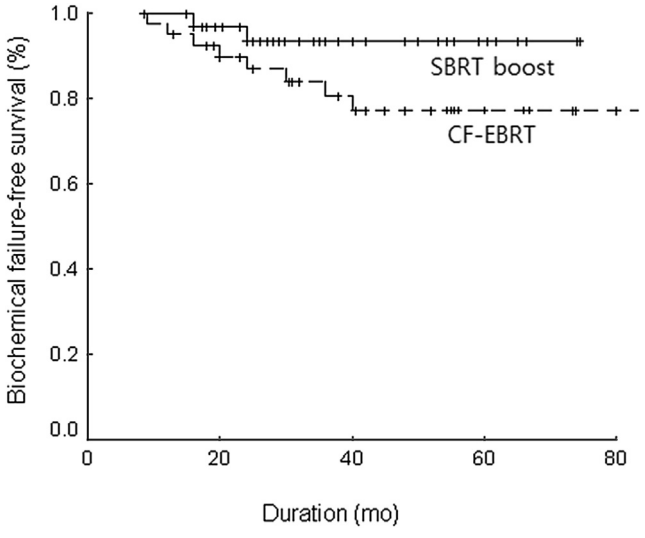

Fig. 3. Biochemical failure free survival after stereotactic body radiotherapy (SBRT) boost and conventionally fractionated external beam radiotherapy (CF-EBRT).

Shi et al[25] reported that a rapid PSA decline in the 1st year following EBRT is positively associated with prostate cancer-specific mortality. Katz et al[28] demonstrated that PSA declines steadily after treatment and achieves very low mean levels of 0.25 ng/mL within 4–5 years. Anwar et al[20] reported that the PSA slope for SBRT was greater than for CF-EBRT ($P < 0.05$) at 2 and 3 years following radiotherapy. This was consistent with our results. A moderate PSA decline of SBRT boost in the 1st year, which is a slower decline compared with that of CF-EBRT, and a steady decline for a duration of 2 years, 3 years, and 4 years resulted in lower PSA nadirs than that of CF-EBRT. A lower PSA nadir and a not rapid but steady PSA decline might lead to favorable BCF free survival in SBRT boost.

Anwar et al[20] compared the PSA kinetics between hypofractionated SBRT and CF-EBRT for localized prostate cancer and reported that the median slopes for SBRT were −0.09 ng/mL/mo, −0.06 ng/mL/mo, and −0.05 ng/mL/mo, respectively, for durations of 1 year, 2 years, and 3 years postradiotherapy. In our study, the rate of PSA decline after SBRT boost combined with WP-EBRT was −0.506 ng/mL/mo, −0.235 ng/mL/mo, −0.129 ng/mL/mo, and −0.092 ng/mL/mo for durations of 1 year, 2 years, 3 years, and 4 years, respectively. Although the direct comparison of rates of PSA decline with other studies is not proper, the rate of PSA decline in our study tends to be more rapid, but the pretreatment PSA level of 9.06 ng/mL in our study was slightly higher than 6.2 ng/mL in the report of Anwar et al.[20] Shi et al[25] described that a lower PSA at diagnosis had a lower PSA velocity following radiotherapy. High pretreatment median PSA might influence the slope of PSA decline. However, the difference in rate of PSA decline after radiotherapy may, due to underlying biologic differences between Asian and Western men, but any racial differences in PSA kinetics after hypofractionated radiotherapy, need further studies.

Recent clinical evidence has demonstrated that the α/β ratio of prostate cancer may be around 2 Gy.[4,5] SBRT boost (3 fractions of 7 Gy) after WP-EBRT (25 fractions of 1.8 Gy) delivered a Biologic Equivalent Dose (BED) of 180 Gy, assuming an α/β ratio of 2 (e.g., BED2), compared with a BED2 of 133.4–143.6 Gy with CF-EBRT (39–42 fractions of 1.8 Gy). Consistent with dose escalation trials which have shown a lower PSA nadir with increased total dose,[29]

we expect the SBRT boost after WP-EBRT regimen to produce a lower PSA nadir and a continuative decline of PSA. In our study, the PSA decline of SBRT boost was not significantly notable in the 1st year, but constantly decreased during periods of 2 years, 3 years, and 4 years to achieve lower PSA nadir than that of CF-EBRT. Lamb et al[30] showed that the postradiation nadir PSA is the strongest indicator. Zelefsky et al[31] demonstrated that nadir PSA values of $\leq$ 1.5 ng/mL at 2 years after radiation therapy for prostate cancer predict for long-term distant metastases and cause-specific mortality. We regard the low nadir of 0.29 ng/mL in SBRT boost after WP-EBRT as indicative of a favorable outcome. Constant declines of PSA for durations of 1 year, 2 years, 3 years, and 4 years and lower PSA nadirs led to favorable BCF free survival, despite the limited follow-up.

Lin et al[32] reported results on toxicity using WBRT and SBRT boost for high-risk prostate cancer. During radiotherapy, 27% of patients had Grade 2 GU toxicity, 12% had Grade 2 acute GI toxicity, there was no Grade 3 acute toxicity noted, and there was no Grade 3 late GU and GI toxicity at last follow-up.

Our study is limited by the retrospective nature of the analysis and the small number of patients. There were no strict protocols for the clinical decision-making process. Future studies should employ more comprehensive instruments to assess the effect of prostate SBRT.

In this report of localized prostate cancer, a continuously greater rate of decline in PSA for durations of 2 years, 3 years, and 4 years following SBRT boost after WP-EBRT resulted in lower PSA nadirs compared with CF-EBRT. The improved PSA kinetics of SBRT boost over CF-EBRT led to favorable BCF free survival. Although follow-up of SBRT boost is limited due to its recent start in the clinic, the improved PSA kinetics of SBRT boost over CF-EBRT are promising for control of prostate cancer.

Conflicts of interest

The authors have no conflicts of interest or financial ties to disclose.

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