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Long-term outcome of whole pelvis radiotherapy and stereotactic body radiotherapy boost for intermediate and high risk prostate cancer

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► ***Original article***

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ABSTRACT

Background: We report our long-term outcomes with Cyberknife to deliver hypofractionated SBRT boost combined with EBRT to patients with intermediate to high risk prostate cancer. ***Materials And Methods***: From March 2008 to July 2014, 42 patients with newly diagnosed, intermediate (73.8%, 31) and high risk (26.2%, 11) localized prostate cancer were treated with EBRT and SBRT boost. The whole pelvis dose was 45 Gy (25 fractions of 1.8 Gy) and the SBRT boost dose was 21 Gy (3 fractions of 7 Gy). ***Results:*** With a median follow-up duration of 84.2 months (range, 20-139.6), the median PSA decline rates were -0.605, -0.229, -0.166 and -0.094 ng/mL/month, respectively, for durations of 1, 2, 3 and 4 years after radiotherapy and has remained near plateau. Four BCFs were observed only in high risk group. The actuarial 8 year BCF free survival and overall survival were 90.3 % and 83.7 %, respectively. BCF-free survival at 8 years were 100 % and 77.8 % for intermediate and high risk group, respectively (p=0.014). No grade 3 or 4 acute and late genitourinary (GU) and gastrointestinal (GI) toxicities were observed. Acute grade 2 GU toxicities were seen in 23.8 % (n = 10) and acute grade 2 GI toxicities in 21.4 % (n = 9). Late grade 2 GU toxicities were observed in 11.9 % (n = 5) and grade 2 GI toxicities in 14.2 % (n = 6). ***Conclusions:*** We demonstrated that SBRT boost after EBRT in intermediate- and high-risk prostate cancer had favorable outcomes with tolerable toxicities.

INTRODUCTION

Prostate cancer is the most prevalent malignancy among male in the United States [1]. Conventional fraction external beam radiation therapy (EBRT) is considered as a standard treatment. Recently, several randomized prospective trials have demonstrated that dose-escalated radiotherapy improves biochemical failure (BCF) free survival [2-4]. Some studies have reported that combination therapy of whole pelvis (WP) EBRT and brachytherapy (BT) boost showed superior biochemical control compared with that of dose-escalated EBRT alone [5-7]. Anyway, BT has several disadvantages such as invasiveness, insertion of multiple catheters, pain and need for anesthesia. In an effort to maximize the benefit of administrating high dose and patient acceptance, stereotactic body radiation therapy (SBRT) is emerging as an alternative radiation therapy technique to deliver dose-escalated radiation to the prostate as a boost [8-9]. Cyberknife robotic radiosurgery system (Accurary Incorporated, synnyvale, CA, USA) is one of them. Many studies reported that dose distribution of Cyberknife resembles with that of BT[1] [10,11].

Currently, SBRT has been tested extensively for low and intermediate risk prostate cancer with treating only prostate and proximal seminal vesicles [12-14]. There are limited data on SBRT boost after WP EBRT in locally advanced prostate cancer. Moreover, there are few reports of long-term follow up. In Inha University Hospital, the combination therapy of WP EBRT and SBRT boost for locally advanced prostate cancer was initiated in 2008. The present study aimed to analyze the 8-year long-term efficacy and toxicities and prostate-specific antigen (PSA) kinetics for patients with intermediate and high risk prostate cancer treated with SBRT boost after WP EBRT.

MATERIALS AND METHODS

We retrospectively reviewed the charts of the patients treated definitively for intermediate and high risk prostate cancer treated with Cyberknife from 2008 to 2014. Forty-two patients, who were newly diagnosed with localized prostate cancer treated with SBRT boost after WP EBRT, were enrolled in this retrospective analysis. All the patients were histologically confirmed as 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

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symptom relief was allowed. Patients were stratified according to 2.2014 National Comprehensive Cancer Network (NCCN) risk stratification guidelines [15]. The study was approved by the Ethical Committee for Clinical Trials of Inha university hospital (approved number: 2019-03-019).

Whole pelvis radiotherapy and SBRT boost treatment planning and delivery

All patients had at least four gold fiducials placed in the prostate prior to treatment planning. To allow the fiducial stabilization, planning imaging was performed at least 1 week after fiducial placement. EBRT and SBRT boost treatment planning were based on the thin-slice CT images (1–2 mm in thickness). MRI fusion was utilized as a supplement for anatomical contour delineation.

The prostate gland, the seminal vesicles and the area of radiographic extracapsular extension were defined as the clinical target volume (CTV) 1. CTV2 included external iliac nodes, internal iliac nodes, presacral nodes and obturator nodes following the Radiation Therapy Oncology Group (RTOG) consensus [16]. The planning target volume (PTV) 1 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 beyond the CTV2 in all directions. The prescription dose of EBRT to the PTV1 and the PTV2 were 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 EBRT treatment plans were generated on Varian Eclipse treatment planning system (version 8.8.6,Varian Medical Systems, Palo Alto, CA, USA).

The prostate gland, the seminal vesicles and the area of radiographic extracapsular extension were defined as the SBRT boost CTV that was the same as that of the EBRT treatment plans. The SBRT boost 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 was 21 Gy, delivered in three fractions and was prescribed to the SBRT boost 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, 1.21–1.43]). 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. All SBRT boost treatment plans were generated on MultiPlan (version 2.2.0, Accuray Incorporated, USA). Treatments were given over three consecutive days.

Follow-up, toxicity scoring and statistical analysis

Patients were followed every 3 months during the first year and every 6–12 months thereafter. Prostate -specific antigen (PSA) levels were obtained at each follow-up. In order to assess PSA kinetics in response to radiotherapy alone, we stopped follow up on the PSA evaluation if they failed by Phoenix definition [17]. All patients had at least 1 year of follow-up. PSA bounce was defined as an absolute increase of 0.2ng/ml from the previous PSA level, followed by a subsequent decrease [18]. The slope of PSA change (ng/mL/month) was calculated as the regression coefficient in a linear regression model for each individuals. The t test was performed to compare mean values and ANOVA in continuous variables. 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).

RESULTS

The median follow-up duration was 84.2 months (range, 20 to 139.6 months). All forty-two patients completed the treatment. The median age was 69 ± 8.06 years (range, 60 to 78 years). Patient characteristics are summarized in table 1.

The median pretreatment serum PSA of 8.98 ng/mL (range, 3.45-29.32 ng/mL). Figure 1 and table 2 shows PSA changes over times, with the different rate of PSA decline for each time intervals since the end of radiotherapy. The slope for all cohorts was maximal in the first year, but tapered off quickly in the following years, with median values of -0.602, -0.229, -0.166, -0.094 and 0.021 ng/mL/month for durations of 1, 2, 3, 4 and 5 years after radiotherapy, respectively. The decline rate of PSA remained nearly plateau after 3 years after radiotherapy.

The continuous PSA decline resulted in low median PSA nadir of 0.16 ng/mL (range, 0.04-1.27) with median 53 months (figure 1). There was no statistically significant difference between intermediate risk patients (0.21 ng/ mL) and high risk patients (0.16 ng/mL) in median nadir (p=0.298). There were no significant differences in the comparison of the nadir by the Gleason score (≤7 versus ≥8; 0.17 versus 0.15 ng/mL; p=0.088). Patients with lower initial PSA (< 10 ng/mL) resulted in significantly lower median PSA nadir (0.16 ng/mL vs 0.20 ng/mL, P = 0.015). Benign PSA bounces were common with 28.6 % (n=12) of all patients. The median time to PSA bounce was 12 months (range, 6–25). The median height of PSA bounce was 0.26 ng/mL (range, 0.21–0.58).

Four BCFs were observed only in high risk group. The actuarial 8 year BCF free survival and overall survival were 90.3 % and 83.7 %, respectively (figure 2). BCF-free survival at 8 years were 100 % and 77.8 % for intermediate and high risk group, respectively (p=0.014) (figure 3). BCF was not observed in patients with PSA bounce, the 8 year BCF-free survival was 100 % for patients with PSA bounce

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versus 86.4 % for the patients without PSA bounce (p=0.715). All other variables, T stage (P = 0.75) was not statistically significant for BCF but Gleason score ≥8 (P =0.05) and large initial PSA (continuous) (p=0.026) was negative predictor on univariate analysis. But on the multivariate analysis, initial PSA (p=0.066) and Gleason score (p=0.955) showed no statistically significant impact on BCF free survival.

Table 3 shows the late genitourinary (GU) and gastrointestinal (GI) toxicities. The most common acute complaints were urinary frequency and urinary obstructive symptoms. No grade 3 or 4 acute genitourinary (GU) and gastrointestinal (GI) toxicities were observed. Acute grade 2 GU toxicities were seen in 23.8 % (n = 10) and acute grade 2 GI toxicities in 21.4 % (n = 9). Acute toxicities were usually resolved within 1–2 months on basic symptomatic therapy. Late grade 2 GU toxicities were observed in 11.9 % (n = 5) and grade 2 GI toxicities in 14.2 % (n = 6). Late GU symptoms included nocturia and urinary frequency which were usually controlled by an alpha receptor antagonist. Five patients experienced grade 2 GI toxicities secondary to rectal bleeding. One patient improved without treatment and four patients improved after laser coagulation. Late toxicity rate was acceptable without severe grade 3 GU and GI toxicities.

Table 1. Patient characteristics (n=42).

variables		
Median age (range)		69±5.08 (60-78)
ECCG		
	0	26 (61.9%)
	1	16 (38.1%)
T stage		
	T1-T2a	4 (9.5%)
	T2b-T2c	34 (81.0%)
	T3a	4 (9.5%)
Gleason score		
	≤6	5 (11.9%)
	7	23 (54.8%)
	≥8	14 (33.3%)
pretreatmetn PSA (ng/mL)		
	median (range)	8.98±6.08 (3.45-29.32)
	<10	23 (54.8%)
	≥10	19 (45.2%)
NCCN risk group		
	intermediate	31 (73.8%)
	high	11 (26.2%)
Abbreviations; ECCG: Eastern Cooperative Oncology Group; PSA: Prostate-specific antigen; NCCN: National Comprehensive Cancer Network;		

Table 2. Prostate specific antigen (PSA) kinetics after stereotactic body radiotherapy boost and whole pelvis external beam radiotherapy.

Variables	
Median PSA nadir (ng/mL)	0.16±0.25 (0.04-1.27)
PSA nadir ≤ 0.5ng/mL	34 (81.0 %)
Median time to nadir (months)	53±11.63 (19.3-78.7)
PSA bounce	12 (28.6%)
Median height of PSA bounce (ng/mL)	0.26±0.12 (0.21-0.58)
Median time to bounce (months)	12±4.70 (6-25)

Table 3. Acute and late genitourinary and gastrointestinal toxicity.

		Grade			
		I	II	III	IV
Acute	Genitourinary	47.6%	23.5%	-	-
	Gastrointestinal	28.6%	21.4%	-	-
Late	Genitourinary	16.7%	11.9%	-	-
	Gastrointestinal	21.4%	14.3%	-	-

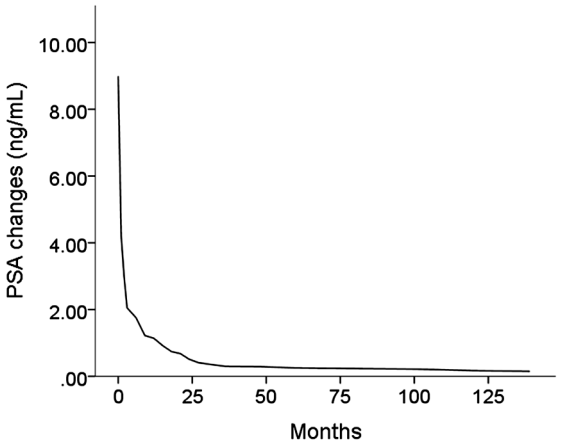


Figure 1. Prostate-specific antigen (PSA) changes after radiation therapy.

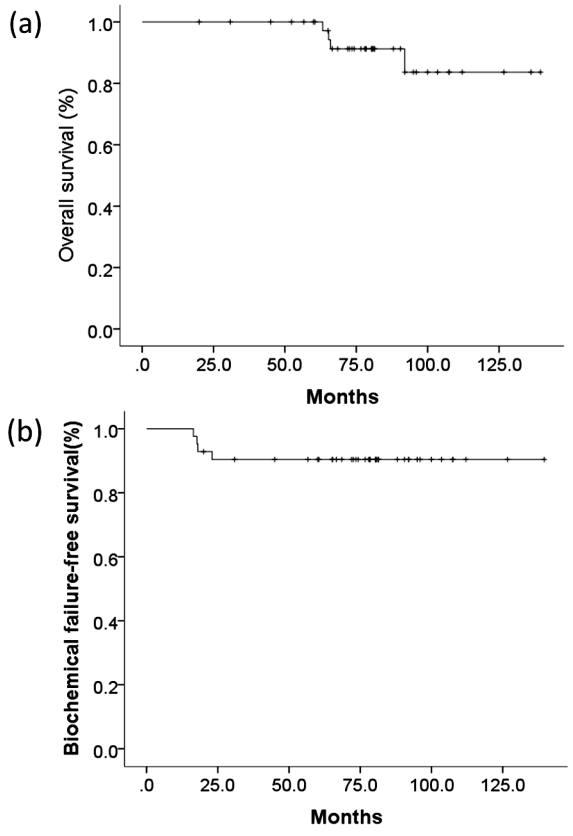


Figure 2. The 8 years overall survival rates **(a)** and biochemical failure-free survival rates **(b)** in all patients were 90.3% and 83.7%, respectively.

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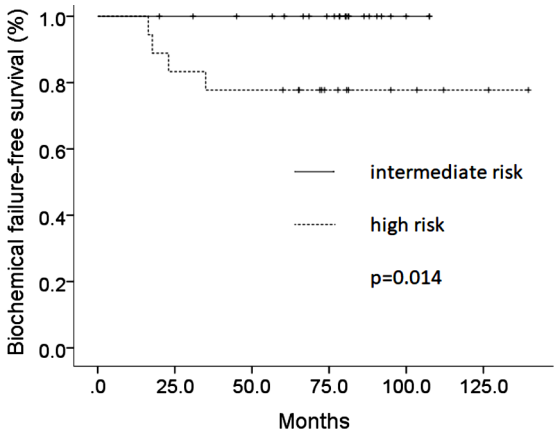


Figure 3. Biochemical failure-free survival rates in the intermediate and high risk groups at 8 years were 100% and 77.8%, respectively (p=0.014).

DISCUSSION

In the present study, we reported long-term analysis of effectiveness and toxicities for patients with localized prostate cancer treated with SBRT boost instead of BT boost after WP EBRT. The BT boost combine with EBRT had shown promising results compared with EBRT alone for intermediate and high risk prostate cancer [6,7,19]. The ASCENDE-RT trial (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) trial is a randomized comparison of 2 methods of dose escalation in the context of combined modality therapy for National Comprehensive Cancer Network high and intermediate risk prostate cancer that included 12 months of androgen deprivation therapy and whole pelvic irradiation to 46 Gy. Compared with a ^{125}I BT boost, patients randomized to an external beam radiation therapy boost to a total of 78 Gy were twice as likely to have experienced biochemical failure at a median follow-up of 6.5 years. The 5-, 7-, and 9-year Kaplan-Meier BCF free survival estimates were 89%, 86%, and 83% for the BT boost versus 84%, 75%, and 62% for the EBRT boost (P<.001)[6].

Despite this, the use of BT continues to decline because several reasons such as introduction of robotic prostatectomy and advancement in the technical sophistication of intensity modulated radiotherapy (IMRT), SBRT and proton therapy [20]. A dosimetric study found that Cyberknife SBRT plans could closely recapitulate BT dosimetry and deliver the plans noninvasively [10,11]. Fuller DB *et al.* compared the dose distribution of high-dose-rate (HDR) BT for prostate cancer with CyberKnife SBRT plans. PTV coverage by the prescription of SBRT plans was similar to that of HDR plans, whereas percent of volume of interest receiving 125% of prescribed radiation dose (V_{125}) and V_{150} values were higher for HDR, reflecting higher doses near HDR source dwell positions. Urethra dose comparisons were lower for SBRT in 9 of 10 cases, suggesting that SBRT may more effectively limit urethra dose. Maximum rectal wall doses were similar, but SBRT created sharper rectal dose falloff beyond the maximum dose region. Second SBRT plans, constructed by equating urethra radiation dose received by point of maximum exposure of volume of interest to the HDR plan, significantly increased V_{125} and V_{150} [11]. Sudahar *et al.* showed substantial difference observed in the core high-dose regions especially in $D_{10\%}$ and $D_{5\%}$ near the BT implants in dosimetric comparison between HDR BT and Cyberknife, although the HDR dose distribution shows a resemblance with that of Cyberknife up to 80% volume doses in the prostate target [10]. In view of these reports, SBRT boost using Cyberknife could be proposed as a non-invasive alternative boost technique instead of brachytherapy. In this study, according to above assumption, SBRT boost was performed using Cyberknife instead of BT.

Katz *et al.* presented 6 year results on 45 high risk prostate cancer patients who were treated with pelvic radiation to 45 Gy followed by SBRT boost of 19-21 Gy in 3 fractions. The actuarial 5 year BCF-free survival was 69% for high-risk patients [21]. Anwar *e al.* evaluated the use of SBRT as a boost in Fifty patients were treated with two fractions of SBRT (9.5-10.5 Gy/ fraction) after 45 Gy EBRT, with 48 eligible for analysis at a median follow-up of 42.7 months. The Kaplan-Meier estimates of biochemical control post-radiation therapy (95 % Confidence Interval) at 3, 4 and 5 years were 95 % (81–99 %), 90 % (72–97 %) and 90 % (72–97 %), respectively [22]. Lin *et al.* also reported 4-year results of SBRT boost for high risk localized prostate cancer. The whole pelvis dose was 45 Gy (25 fractions of 1.8 Gy). The SBRT boost dose was 21 Gy (three fractions of 7 Gy). Ninety percent of these patients received hormone therapy. The estimated 4 year BCF-free survival was 91.9%. Three BCFs were observed [9]. In our study, BCF-free survival at 8 years were 100 % and 77.8 % for intermediate and high risk group, respectively (p=0.014). Four BCFs were observed only in high risk group. To the best of my knowledge, our study is the first reported long-term clinical outcome, with median follow-up duration of 84.2 months, of SBRT boost using Cyberknife after WP EBRT for intermediate and high risk prostate cancer.

Pryor *et al.* reported the early toxicity following gantry-based, SBRT boost within a prospective, phase 2, multicenter study (PROMETHEUS: ACTRN12615000223538). Acute grade 2 GI and GU toxicity occurred in 4.4 and 26.6% with no acute grade 3 toxicity. At 6, 12, 18, 24, and 36 months post-treatment the prevalence of late grade ≥2 GI toxicity was 1.6, 3.7, 2.2, 0, and 0%, respectively, and the prevalence of late grade ≥2 GU toxicity was 0.8, 11, 12, 7.1, and 6.3%, respectively. Three patients experienced grade 3 late toxicity at 12 to 18 months which subsequently resolved to grade 2 or less [23]. Pasquier *et al.* also assessed toxicity with

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hypofractionated stereotactic boost after conventional radiotherapy in intermediate risk prostate cancer (CKNO-PRO). A first course delivered 46 Gy by IMRT (68.4% of patients) or 3D conformal radiotherapy (31.6% of patients). The second course delivered a boost of 18 Gy (3x6Gy) within 10 days. Grade ≥2 acute GI and GU toxicities were 13.2% and 23.7%, respectively. Grade ≥2 late GI and GU toxicities were observed in 6.6% and 2.6% of patients, respectively. No grade 4 toxicity was observed [24]. However, in this study, no grade 3 or higher GI and GU toxicities were not observed and no urethral strictures at last long-term follow-up. Our study showed the similar proportion of toxicities.

Despite our encouraging results with long-term follow-up demonstrating the feasibility of SBRT boost after EBRT, our study is limited by retrospective nature of analysis and small number of patients. Currently, NCT01985828 is recruiting participants to evaluate the effectiveness of Cyberknife SBRT as monotherapy or boost therapy in intermediate or high risk localized prostate cancer. Future studies should employ more comprehensive instruments to assess the effect of prostate SBRT.

The outcomes of SBRT boost after EBRT in intermediate and high risk prostate cancer was very encouraging. The biochemical disease control is comparable to other available therapies, with equal to or better toxicity profiles. We look forward to future multicenter studies that will examine outcomes with this treatment approach.

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Author contribution: None.

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