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Clinical outcome of stereotactic body radiotherapy for localized prostate cancer: long-term results

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► ***Original article***

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ABSTRACT

Background: Stereotactic body radiotherapy (SBRT) is an emerging treatment option which allows for extreme hypofractionation using modern technologies, because the low α/β-ratio favors the use of high dose per fraction in prostate cancer. There is a need for more data about SBRT. We provide a long-term update of SBRT clinical outcome using CyberKnife for the treatment of localized prostate cancer. ***Materials and Methods:*** This study was based on a retrospective analysis of 43 patients treated with SBRT using CyberKnife for localized prostate cancer (23.3% in low risk, 67.4% in intermediate risk and 9.3% in high risk). The target volume included the prostate with or without the seminal vesicles depending on the risk stratification and uncertainty margins that are kept at 3-5 mm. Total dose of 36.25 Gy in 5 fractions of 7.25 Gy were administered. ***Results:*** 43 patients with a median 73.6 months (range, 14 to 119 months) follow-up were analyzed. There was three biochemical failure (BCF). Eight-year BCF free survival and overall survival were 92.0% and 73.1%, respectively. Median PSA decline rates were -0.301, -0.191 and -0.115 ng/mL/month, respectively, for durations of 1, 2 and 3 years after radiotherapy and has remained plateau. Median PSA nadir was 0.27 ng/mL at median 38 months and PSA bounce (median 0.33 ng/mL) occurred in 32.6% (n = 14) of patients at median 19 months after SBRT. There was no grade 3 acute and late toxicity. ***Conclusion:*** Our long-term experience with SBRT using CyberKnife for localized prostate cancer demonstrates favorable efficacy and toxicity.

Keywords: *CyberKnife, prostate cancer, stereotactic body radiotherapy, prostate-specific antigen, radiotherapy, hypofractionation.*

INTRODUCTION

Prostate Cancer is the most common malignant tumor among men worldwide [1]. As the prevalence of prostate cancer increases, various treatment modalities are considered [2]. Although intensity-modulated radiation therapy (IMRT) is the standard external beam modality for clinically localized prostate cancer, Stereotactic body radiotherapy (SBRT) is an emerging treatment option which allows for extreme hypofractionation using modern technologies [3-6]. Clinical evidence suggests that the α/β ratios of prostate cancer is maybe around 1.5 Gy and lower than the surrounding normal tissue [7, 8]. One phase III study trial suggested that hypofractionation regiment of 62 Gy in 20 fractions in safe and acute and late complication were equivalent to that of the conventional fractionationated regimen of 80 Gy in 40 fractions [9].

The Cyberknife is one of the tools for hypofractionated SBRT and real-time image guidance to account for intrafraction prostate motion. Advanced technique of Cyberknife allows high doses of radiation to be delivered precisely to the target while sparing the surrounding healthy tissue, thus achieving high biochemical control and low toxicity [1, 4, 5]. The hypofractionated radiotherapy schema may

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improve the biochemical control of prostate cancer without increasing toxicities associated with late-responding tissue [3, 10]. Reports on short-term biochemical outcomes of this center have been previously reported [11].

Serum PSA is a well-established tumor marker for screening prostate cancer and monitoring response after treatment. The PSA change after radiotherapy has been extensively studied and several parameters such as PSA nadir, time to nadir or PSA velocity have been proposed as predictive factors for treatment outcome [12,13]. However, the PSA kinetics after SBRT have not been fully studied during long-term follow-up period.

We report our long-term follow-up experience with SBRT, evaluating the long-term outcome and assessing the PSA kinetics in treating patients with localized prostate cancer.

MATERIALS AND METHODS

We retrospectively reviewed the charts of patients treated definitively for localized prostate cancer treated with Cyberknife from 2008 to 2018. Forty-three patients newly diagnosed with localized prostate cancer treated SBRT using the Cyberknife robotic radiosurgery system 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 before recurrence was proved. Prior transurethral resection of the prostate for urinary symptom relief was allowed. Patients were stratified according to 2.2014 NCCN risk stratification guidelines [14]. The study was approved by the Ethical Committee for Clinical Trials of our institution and the retrospective data was collected in our institutional database. In order to assess prostate-specific antigen (PSA) kinetics, in response to radiotherapy alone, we stopped follow up on the PSA evaluation if they failed by Phoenix definition [15]. 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 [16].

SBRT treatment planning and delivery

Three to four gold fiducial markers were implanted trans-perineally into the prostate under transrectal ultrasound guidance. On one week after fiducial placement, treatment planning CT scans with contrast enhanced were performed at a slice thickness of 1.5 mm using a multi-slice scanner (Lightspeed 16, GE Medical Systems, USA). MRI scans (Signa HDxt, GE Medical System, USA) were obtained with sequences of T1-weighted, gadolinium-enhance. Fused CT and MRI were used for the treatment planning. Patients had bowel preparation to eliminate rectal contents before treatment-planning scans. All patients underwent computed tomography (CT) simulation in the supine position. A vacuum bag and an ankle holder device was employed as a patient immobilization device. Fused CT and MR images were used for the treatment planning. The prostate, seminal vesicles, rectum, bladder, penile bulb, and bowel were contoured. The clinical target volume (CTV) included the prostate with or without the proximal seminal vesicles. The planning target volume (PTV) equaled the CTV expanded 3mm posteriorly and 5 mm in all other dimensions. The prescription dose was 36.25 Gy, delivered in 5 fractions, was prescribed to the PTV. Inverse treatment planning was conducted using the MultiPlan CyberKnife treatment planning system ver. 2.2.0 (Accuray Inc., Sunnyvale, CA, USA). Treatments were performed on 5 consecutive days. The prescription dose covered at least 95% of the PTV, normalized to the 75%–85% isodose line (mean homogeneity index of 1.26 [range, 1.21 to 1.41]). The HI describes the uniformity of dose within a treated target volume and is directly calculated from the prescription isodose line chosen to cover the margin of the tumor: HI = maximum dose / prescription dose. 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 patients were treated with the CyberKnife G4 system (Accuray Inc., Sunnyvale,

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CA, USA), composed of a 6-MV linear accelerator mounted on a robotic arm, with two orthogonal kV X-ray imagers that provide real-time stereoscopic image guidance and automatic correction for movements of the prostate throughout treatment with motional tracking system of CyberKnife. Treatments were given over 5 consecutive days. Androgen deprivation therapy was not applied to anyone.

Follow-up 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. PSA bounce was defined as an absolute increase of 0.2 ng/mL from the previous PSA level, followed by a subsequent decrease [17]. Toxicity was documented at follow-up visits using the Radiation Therapy Oncology Groups. Acute toxicity was defined as occurring within 6 months of completing treatment, and late toxicity as those events occurring later than 6 months. The *t-test* was performed to compare mean values and ANOVA in continuous variables. Biochemical failure (BCF) free survival was estimated using the Kaplan-Meier methods. Statistical analysis was performed using IBM SPSS ver. 19.0 (IBM, Armonk, NY, USA).

RESULTS

The median follow-up duration was 73.6 months (range, 14 to 119 months). All forty-three patients completed the treatment. The median age was 68 years (range, 55 to 77 years). Patient characteristics are summarized in table 1.

The median pretreatment serum PSA of 7. ng/mL (range, 3.45 to 21.34 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 -0.301, -0.191, -0.125, -0.025 and 0.009 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 0.27 ng/mL (range, 0.04-1.44) with median 38 months (table 3). There was no statistically significant difference between low risk patients (0.14 ng/ mL) and intermediate-high risk patients (0.48 ng/mL) in median nadir (p=0.182). There were no significant differences in the comparison of the nadir by the Gleason score (≤6 versus 7; 0.23 versus 0.38 ng/mL; p=0.346) and pre-treatment PSA (≤10 versus >10; 0.18 versus 0.41; p=0.087). Benign PSA bounces were common with 32.6 % of all patients. The median time to PSA bounce was 19 months (range, 6-27). The median height of PSA bounce was 0.33 ng/mL (range, 0.21-1.39).

Three BCF was observed. One was in intermediate risk group and two were in high risk group. The actuarial 8-year BCF free survival and overall survival were 92.0% and 73.1%, respectively. Figure 2 depicts Kaplan-Meier estimates of BCF-free survival at 8 years were 100%, 96% and 50% for low, intermediate and high- risk group, respectively (p=0.012). BCF was not observed in patients with PSA bounce, the 8-year BCF-free survival was 100% for patients with PSA bounce versus 88.1% for the patients without PSA bounce (p=0.224). On univariate analysis, initial large PSA (p=0.038) and Gleason score ≥7 (p=0.041) were shown to be negative predictor for BCF. But on the multivariate analysis, initial PSA (p=0.478) and Gleason score (p=0.241) showed no statistically significant impact on BCF free survival.

Table 4 shows the late genitourinary (GU) and gastrointestinal (GI) toxicities. The most common GU toxicities were urinary frequency and urinary obstructive symptoms, Acute grade 2 GU toxicities were seen in 20.9% and usually resolved within 1-2 months on basic symptomatic therapy. Rectal pain was most frequent GI toxicities and acute grade 2 GI toxicities were 23.3%. Acute GI toxicities were resolved within 1-2 months with pain medication. No grade 3 late GU and GI toxicities

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were noted. Late grade 2 GU toxicities were observed in 7.0% and grade 2 GI toxicities in 9.3%. Late GU symptoms included nocturia and urinary frequency which were usually controlled by an alpha receptor antagonist. Four patients experienced rectal bleeding at 3-6 months after treatment. One patient improved without treatment and three patients improved after laser coagulation.

Table 1. Patients characteristics (n=43).

Variables	
Median age (range)	68 (55-77)
ECGO scael	
0	29 (67.4%)
1	14 (32.6%)
T stage	
T1-T2a	13 (30.2%)
T2b-T2c	30 (69.8%)
Gleason score	
≤6	15 (34.9%)
7	24 (55.8%)
≥8	4 (9.3%)
Pretreatment PSA (ng/mL)	
median (range)	7.31 (3.45-21.3)
≤10	30 (69.8%)
>10	13 (30.2%)
NCCN risk group	
low	10 (23.3%)
intermediate	29 (67.4%)
high	4 (9.3%)
NCCN, National Comprehensive Cancer Network.	

Table 2. Median rate of PSA decline following stereotactic body radiotherapy.

Through year	slop of PSA decline
1	-0.301±0.087
2	-0.191±0.065
3	-0.115±0.053
4	-0.075±0.057
5	-0.025±0.021

Table 3. Prostate-specific antigen (PSA) kinetics following stereotactic body radiotherapy.

Variables	
Median PSA nadir	0.27 ng/mL (0.04-1.44)
PSA nadir ≤ 0.5ng/mL	30 (69.8%)
Median time to nadir	38 months (9-56)
PSA bounce	14 (32.6%)
Median height of PSA bounce	0.33 ng/mL (0.21-1.39)
Median time to bounce	19 months (6-27)

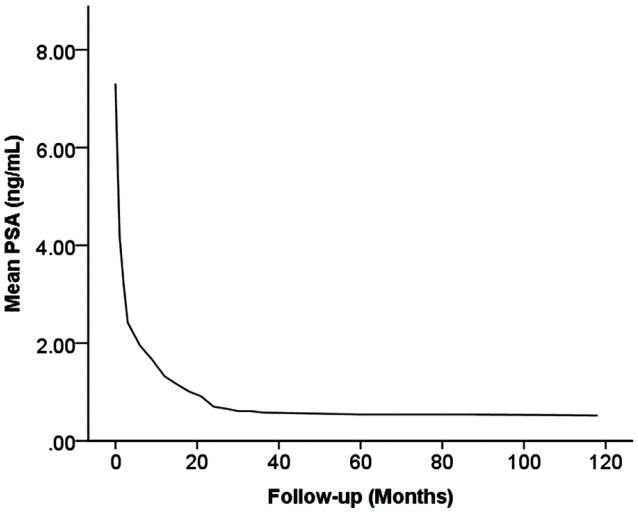

Figure 1. Prostate-specific antigen changes after stereotactic body radiotherapy.

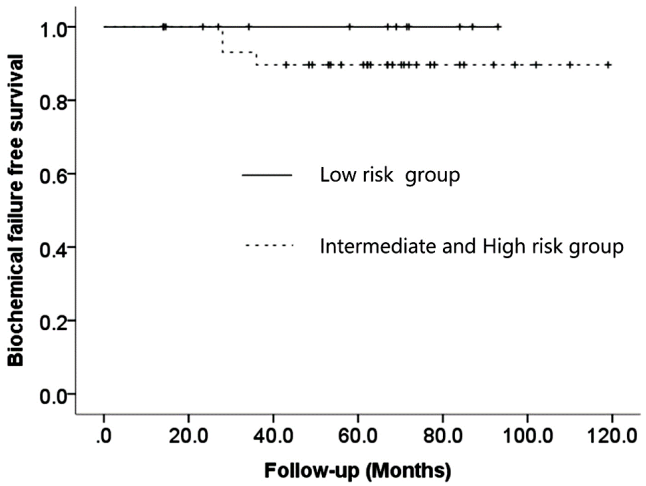

Figure 2. Kaplan-Meier curves for biochemical failure free survival according to risk group.

Table 4. Toxicity (unit, %).

	Grade		
	I	II	III
Acute			
GU	37.2	20.9	-
GI	27.9	23.3	-
Late			
GU	11.6	6.1	-
GI	13.9	9.3	-

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DISCUSSION

This article reports the long-term BCF free survival, PSA level change and late toxicity outcomes for localized prostate cancer. Our study demonstrates excellent long-term control with low toxicities. Lieng *et al.* reported the result of 96 patients with localized prostate cancer received image-guided IMRT to a dose of 66 Gy in 3 Gy fractions in a phase II trial and 8-year biochemical free survival rates was 80% [18]. Teh *et al.* treated *596* patients with cT1-T3 prostate cancer under IMRT using a moderated hypofractionation regimen (76.7 Gy at 2.19 Gy/fraction) and for low-, intermediate-, and high-risk patients the 10-year bRFS rates were 91.4%, 89.3%, and 76.2%, respectively [19]. Wilson *et al*. reported 207 localized prostate patients treated with Iodine-125 permanent interstitial implantation and Ten-year BCF-free survival by pre-treatment risk group were 96% for low-risk, 83% for intermediate-risk and 50% for high-risk disease [20]. Katz and Kang reported outcomes for 515 patients (324 with low risk, 153 with intermediate risk, and 38 with high risk) with localized prostate cancer treated with a regimen of five -fraction SBRT to dose of 35-36.25 Gy [21]. With a median follow-up of 84 months, the 8-year disease-free survival was 93.6, 84.3, and 65.0% for low, intermediate, and high-risk group patients, respectively. Our the 8-year actuarial BCF-free survival rate of 92% compares favorably with that obtained with IMRT, brachytherapy and SBRT.

Katz reported the PSA change of low risk prostate cancer according to period after SBRT. The median PSA dropped to 0.1 by five years and has remained there [22]. Our outcome showed similar PSA decline graph. Median PSA decline rates has remained plateau after 3-year follow-up.

Toxicity following SBRT was similar to that of EBRT or brachytherapy. Zelefsky *et al.* [23] reported result on late toxicity using 81 Gy dose with IMRT in conventional fractionation. The 8-year actuarial likelihood of grade 2 GI toxicity was 1.6% and 0.1% of patients experienced grade 3 rectal toxicity. The 8-year likelihood of late grade 2 and 3 GU toxicities were 9% and 3%, respectively. Katz and Kang [24,25] reported no acute RTOG grade 2-4 toxicity, with late grade 3 GU toxicity in 1.7% of patients. Our current study shows the similar proportion of toxicity.

Our study is limited by 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.

The decline rate of PSA showed gradual decline and remained nearly plateau after 3 years after SBRT. The outcomes of our study 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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***Conflicts of interest*: Declared none.**

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