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Prostate-specific antigen kinetics following hypofractionated stereotactic body radiotherapy for low- and intermediate-risk prostate cancer ☆

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ABSTRACT

Background: Stereotactic body radiotherapy (SBRT) has emerged as an effective treatment for localized prostate cancer. However, prostate-specific antigen (PSA) kinetics after SBRT has not been well characterized. The objective of the current study is to analyze the rate of PSA decline and PSA nadir following hypofractonated SBRT in low- and intermediate-risk prostate cancer.
Methods: From 2008 to 2014, 36 patients newly diagnosed, low- and intermediate-risk (NCCN definition) prostate cancer were treated with SBRT using Cyberknife. Total dose of 36.25 Gy in 5 fractions of 7.25 Gy were administered. No one received androgen deprivation therapy (ADT). PSA nadir and rate of change in PSA (slope) were calculated and compared.
Results: With a median follow-up of 52 months (range, 13–71), the median rates of decline of PSA were −0.359, −0.199 and −0.127 ng/mL/month, respectively, for durations of 1, 2 and 3 years after radiotherapy, respectively. The decline of PSA was maximal in the first year and continuously decreased for durations of 2 and 3 year. The median PSA nadir was 0.27 ng/mL after a median 33 months. 5-year biochemical failure (BCF)-free survival was 100% for low- and intermediate-risk patients.
Conclusions: In this report of low- and intermediate-risk prostate cancer, continuous decrease of PSA level for duration 1, 2 and 3 year following SBRT using Cyberknife resulted in lower PSA nadir. Also, SBRT leaded to long-term favorable BCF-free survival in low- and intermediate-risk prostate cancer.

1. Introduction

Prostate cancer is the most common cancer and the second leading cause of death from among men in the United States [1] and the incidence rate in Korea is relatively lower than those in western nations but continue to increase annually owing to the aging of society, adoption of westernized lifestyle, and adding 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 conventional treatment option for localized prostate cancer [3]. According to the modern understanding of radiobiology, the α/β ratios of prostate cancer is may be around 1.5 Gy and the lower than the surrounding normal tissue [4,5]. The hypofractionated radiotherapy schema may improve the biochemical control of prostate cancer without increasing toxicities associated with late-responding tissue [4]. One phase III study trial suggested that hypofractionation regiment of 62 Gy in fractions is safe and acute and late complication were equivalent to that of the conventional fractionationated regimen of 80 Gy in 40 fractions [6].

The Cyberknife (Accuray, Sunnyvale, CA, USA) is one of the tools for hypofractionated SBRT and real-time image guidance to account for intrafraction prostatic 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 [7–9]. For low and intermediate risk prostate cancer, recent published literature support use of hypofractionated SBRT using Cyberknife with excellent 5 year biochemical control rates and correspondingly acceptable rates of toxicity [7,10].

Prostate-specific antigen (PSA) is well-established biomarker for prostate cancer and available for monitoring response to treatment. In patients without androgen deprivation therapy

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(ADT), analysis of PSA kinetics after treatment could reveal the biologic effect of radiation on prostate cancer. The changes of PSA after EBRT and brachytherapy have been extensively researched [11]. Lower PSA nadir and rapid decline in PSA after treatment have been related to improved clinical outcome [12–15]. While recent studies have demonstrated that a lower PSA nadir (<0.5 ng/mL) has been associated with superior clinical disease-free survival [15,16], 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 negative [11,17–20]. Furthermore, kinetics of PSA decline following SBRT using Cyberknife remains poorly understood and only a few report from western countries [21,22]. It is necessary to elucidate the kinetics of SBRT in Asian population. The objective of the current study is to analyze the rate of PSA decline and PSA nadir following hypofractonated SBRT using Cyberknife in low- and intermediate-risk prostate cancer.

2. Materials and methods

We retrospectively reviewed the charts of patients treated definitively for low- and intermediate-risk prostate cancer treated with Cyberknife from 2008 to 2014. Thirty-six 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. Prior transurethral resection of the prostate for urinary symptom relief was allowed. Patients were stratified according to 2.2014 NCCN risk stratification guidelines [23]. 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 PSA kinetics in response to radiotherapy alone, we stopped follow up on the PSA evaluation if they failed by Phoenix definition [24]. All 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 [25].

2.1. SBRT treatment planning and delivery

Four or more gold fiducial markers were implanted transperineally into the prostate. After seven days, patients underwent magnetic resonance imaging (MRI) and thin-slice CT scan. Fused CT and MRI 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 and proximal seminal vesicles. The planning target volume (PTV) equaled the CTV expanded 3 mm posteriorly and 5 mm in all other dimensions. The prescription dose was 36.25 Gy, delivered in five fractions, was prescribed to the PTV. The prescription dose covered at least 95% of the planning target volume, normalized to the 75–85% isodose line (median homogeneity index of 1.25 [range, 1.23–1.41]). 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 5 consecutive days. Androgen deprivation therapy (ADT) was not applied to anyone.

2.2. Statistical analysis

To eliminate the effect of differing follow-up durations between SBRT boost after EBRT and CF-EBRT, we calculated the rate of decline in PSA over an interval of time from the completion of radiotherapy to 1, 2, 3 and 4 years post-treatment. The slope of PSA change (ng/mL/month) was calculated as the regression coefficient in a linear regression model for each individual. The t test was performed to compare mean values and ANOVA in continuous variables and the Mann–Whiteny test was used to compare distributions of the slop of PSA. 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. Thirty-six patients with a median 52 months (range, 13–71 months) follow-up were analyzed. The median age was 68 years (range, 55–77 years). Patient characteristics are summarized in Table 1.

The pretreatment median PSA level was 7.18 ng/mL (3.45–14.90). Fig. 1 shows PSA changes over times, with the different rate of PSA decline for each time intervals since the end of radiotherapy. To investigate the PSA kinetics after radiotherapy, the rate of PSA decline (slope) was calculated for 3 intervals following radiotherapy (0–1 year, 0–2 years and 0–3 years). The slope for all cohorts was maximal in the first year, but tapered off quickly in the following years, with median values of -0.359, -0.199 and -0.127 ng/mL/month for durations of 1, 2 and 3 years after radiotherapy, respectively. The distribution of the median slopes in intermediate-risk patients (-0.451, -0.178 and -0.132 ng/mL/month, respectively) for 1, 2 and 3 years following radiotherapy did not differ from those in low-risk patients (-0.288, -0.156 and -0.113 ng/mL/month, respectively) ($p=0.103$, $p=0.589$ and $p=0.153$, respectively). Patients with high initial PSA (>10 ng/mL) had greater median rate of PSA decline only during 1 year following radiotherapy than those with low initial PSA (≤ 10 ng/mL) (-0.695 versus -0.313 ng/mL/month, $p=0.030$). Similarly, high Gleason score had greater slope during 1 years (-0.495 versus -0.319 ng/mL/month, $p=0.022$)

All patients were without evidence of biochemical or clinical failure to date and favorable low PSA nadirs have been observed with a current median PSA nadir of 0.27 ng/mL (range, 0.04–1.15) with median 33 months (Table 2 and Fig. 2). There was no statistically significant difference between low-risk patients (0.12 ng/mL) and high-risk patients (0.44 ng/mL) in median nadir ($p=0.107$). There were no significant difference in the comparison of the nadir by the Gleason score (≤ 6 versus 7) and pre-treatment

Table 1
Patient characteristics ($n=36$).

Variables	
Median age (range)	68 (55–77)
ECCG	
0	24 (66.7%)
1	12 (33.3%)
T stage	
T1–T2a	13 (36.1%)
T2b–T2c	23 (63.9%)
Gleason score	
≤ 6	15 (41.7%)
7	21 (58.3%)
Pretreatment PSA (ng/mL)	
Median (range)	7.18 (4.45–14.90)
<10	28 (77.8%)
≥ 10	8 (22.2%)
NCCN risk group	
Low	10 (27.8%)
Intermediate	26 (72.2%)

NCCN, National Comprehensive Cancer Network.