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Prostate-specific antigen bounce after high-dose-rate prostate brachytherapy and hypofractionated external beam radiotherapy

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ABSTRACT

PURPOSE: To report the frequency, timing, and magnitude of prostate-specific antigen (PSA) bounce (PB) in patients who received high-dose-rate (HDR) brachytherapy (HDRB) plus hypofractionated external beam radiation therapy (HypoRT) and to assess a possible correlation between PB and biochemical failure (BF).

METHODS AND MATERIALS: Patients with intermediate-risk prostate cancer received 10 Gy single-fraction ^{192}Ir HDRB followed by 50 Gy in 20 daily fractions of HypoRT without androgen deprivation therapy. All patients had a minimum 2-year followup. The PB was defined as PSA elevation higher than 0.2 ng/mL from previous measurement with subsequent drop to pre-bounce level. The BF was defined as PSA nadir + 2 ng/mL.

RESULTS: A total of 114 patients treated between 2001 and 2009 were eligible for analysis. At a median followup of 66 months, the PB was found in 45 (39%) patients with a median time to bounce of 16 months (range, 3–76 months). The median time to PSA normalization after a PB was 9 months (range, 2–40 months). The median magnitude of PB was 0.45 ng/mL (range, 0.2–6.62). The BF occurred in 12 (10.5%) patients of whom three had a PB. Median time to BF was 52.5 months. Four patients (3.5%) in the PB group fit the criteria for BF.

CONCLUSIONS: The PB is common after HDRB and HypoRT and can occur up to 76 months after treatment. It can rarely fit the criteria for BF. The time to PB is shorter than the time to BF. There is a lower incidence of BF in patients with a PB. An acknowledgment of this phenomenon should be made when interpreting PSA results during followup to prevent unnecessary interventions.

Keywords: Prostate cancer; Intermediate risk; HDR brachytherapy; PSA bounce; Biochemical failure

Introduction

The prostate-specific antigen (PSA) level is widely used to measure treatment success in patients with prostate adenocarcinoma who have undergone radical treatment. In patients who have been treated with radical external beam radiotherapy (EBRT) and/or brachytherapy, there is a gradual decrease in the PSA level. The time to nadir is usually in the order of years rather than months, with the PSA rarely dropping to an undetectable level. Rises in PSA level measurement post-treatment is usually indicative of biochemical failure (BF), and rises with a magnitude of PSA nadir + 2 ng/mL has now been widely adopted as the definition of BF (1). However, a rising PSA after radiotherapy does not necessarily indicate treatment failure. Benign rises in PSA level followed by a subsequent fall without intervention, called a PSA bounce (PB), is a common occurrence after radiation.

The PB was first described in patients who underwent low-dose-rate (LDR) brachytherapy (2, 3) but has since been documented in patients who received EBRT (4). The cause of this phenomenon remains mainly idiopathic, but hypotheses including ejaculation, instrumentation, and radiation prostatitis have been postulated (2, 5).

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The PB has been well documented in many LDR brachytherapy series and has neither been shown to correlate with increased risk of BF nor to predict for future failure (2, 6, 7). Some have even found that PB confers a risk reduction for BF (8).

However, there is a paucity of data on the incidence, timing, and magnitude of PB and its relationship to BF in patients who have had high-dose-rate brachytherapy (HDRB), either alone or combined with EBRT. Furthermore, the few studies that do report on PB in HDRB patients have a relatively short followup period (9).

In this study, we report on the frequency and characteristics of PB in patients with intermediate-risk prostate cancer who received HDRB as a boost to EBRT without the use of androgen deprivation therapy (ADT) and its relationship to BF. We also report on the outcomes of these patients.

Methods and materials

Patient population

In 2001, we started a program of single-fraction HDRB combined with hypofractionated EBRT (HypoRT) in patients with prostate cancer. Between May 2001 and November 2011, 195 patients with histologically confirmed prostate cancer were treated under this program. The patients had intermediate-risk disease, T1–T2 disease; Gleason score of seven or less; and initial PSA (iPSA) level of 20 ng/mL or lower (10). All patients had a negative CT scan of the abdomen/pelvis and bone scan before treatment. Clinical information was retrospectively collected and recorded in a database. Study selection criteria included patients who had a minimum of 2 years followup with at least four PSA results, no BF within the first year, and no ADT.

Treatment

All patients received a combination of HDRB followed by HypoRT without ADT. The procedure has been previously described in detail elsewhere (11). Briefly, the interstitial HDRB procedure was performed under spinal anesthesia when 17 interstitial catheters were implanted into the prostate under transrectal ultrasound guidance. The positions of the catheters were verified postimplant with a CT simulation scan and adjusted if necessary. The prostate, urethra, and rectum were outlined on the CT scan, and the treatment was planned using Plato System (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). A dose of 10 Gy was prescribed to the prostate surface, with no more than 1 cm^3 of urethra receiving a dose higher than 12.5 Gy, no portion of urethra receiving a dose higher than 15 Gy, and no more than 1 cm^3 of rectum receiving a dose higher than 7.5 Gy. Treatment was delivered using a single ^{192}Ir retractable source using a microSelectron HDR afterloading machine (Nucletron, an Elekta company). The catheters were removed after treatment completion, and patients were discharged the same or the next day.

The HypoRT treatment started 7–10 days after HDRB. Patients underwent CT scan simulation in the supine position, with a comfortably full bladder before HDRB implant. An urethrogram was performed to help define the prostatic apex. The clinical target volume was the prostate gland and the proximal third of the seminal vesicle. A 1-cm uniform margin was added for the planning target volume. Patients were treated with three-dimensional conformal radiation therapy using a five-field technique to a dose of 50 Gy in 20 daily fractions, prescribed to the isocenter. Daily ultrasound-based image-guided radiation therapy (Clarity Prostate System, Elekta AB, Stockholm, Sweden; BAT-System, North American Scientific, Chatsworth, CA) was used for correction of interfraction organ motion (12).

PB definition

We chose to use the PSA + ≥0.2 ng/mL, followed by a spontaneous decrease at any point in time to the prebounce level or lower, as the definition of PB as this is the most widely used bounce definition in literature (13). The PB duration was defined as the time between onset of rising PSA and return to prebounce level. We also performed additional analyses using other PSA thresholds, including 0.5 ng/mL or higher and 1 ng/mL or higher. We used the Phoenix definition (1) to identify BF and felt that it would be imperative to report on the frequency of patients with a PB who fit the criteria for BF. Therefore, we also performed analyses on the number of patients whose bounce was 2 ng/mL or greater.

Statistics

Data collected are presented by descriptive statistics; analyses were performed using GraphPad Prism v.5 statistics software (GraphPad Software, San Diego, CA) and Stata v.10.1 (StataCorp LP, College Station, TX). The BF-free survival was calculated using the actuarial Kaplan–Meier method. Univariate analyses were performed using Cox regression. Hazard ratios and 95% confidence intervals were calculated. Statistical significance was considered if p-value was lower than 0.05. This analysis was performed after approval by the Institutional Review Board.

Results

A total of 114 patients fit the inclusion criteria for this study. The median followup time was 66 months (range, 24–124 months). The baseline characteristics are summarized in Table 1. A total of 45 patients (39%) fit the criteria for a bounce. The PB frequency using cutoff levels of 0.5 ng/mL or higher and 1 ng/mL or higher were 25 (21%) and 13 (11%), respectively. Four patients (3.5%) had a PB that fit the criteria for BF with subsequent PSA fall, not characterizing disease progression. The median