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PSA bounce after prostate brachytherapy with or without neoadjuvant androgen deprivation

Samuel D. McGrath, J. Vito Antonucci, Dwight L. Fitch, Michel Ghilezan, Gary S. Gustafson, Frank A. Vicini, Alvaro A. Martinez, Larry L. Kestin*

Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI

ABSTRACT

PURPOSE: To assess the impact of PSA bounce (PB) on biochemical failure (BF) and clinical failure (CF) in brachytherapy patients treated with or without neoadjuvant androgen deprivation (AD).

METHODS AND MATERIALS: From 1987 to 2003, 691 patients with clinical stage T1–T3N0M0 prostate cancer were treated with external beam radiotherapy (EBRT) and high-dose-rate (HDR) brachytherapy boost ($n = 407$), HDR brachytherapy alone ($n = 93$), or permanent seed implant ($n = 191$). Three hundred seventeen patients (46%) received neoadjuvant/adjuvant AD with RT. BF was scored using 3 definitions (ASTRO—3 rises, nadir + 2 ng/ml, and threshold 3 ng/ml) based on current and absolute nadir (AN) methodologies. PB was defined as any increase in PSA followed by a decrease to the prior baseline or lower. The median followup was 4.0 years.

RESULTS: Forty-six patients (7%) experienced CF at 5 years. PB of ≥0.1, ≥1.0, and ≥2.0 ng/ml at any time after RT occurred in 330 (48%), 60 (9%), and 22 patients (3%) respectively. The use of an AN definition reduced the likelihood of scoring PB as BF across all levels. The patients receiving AD experienced significantly longer bounce duration. Bounce <1.0 ng/ml showed no association with CF. For bounce ≥1.0 ng/ml, 10% demonstrated CF vs. 6% without bounce of this amplitude ($p = 0.27$). Bounces ≥1.0 ng/ml were more likely to be scored as BFs for definitions based on current nadir (3 rises: 20% vs. 13%, nadir + 2: 43% vs. 11%, 3 at/after nadir: 57% vs. 12%) than those based on AN (3 rises: 8% vs. 10%, nadir + 2: 18% vs. 11%, 3 at/after nadir: 13% vs. 11%).

CONCLUSIONS: Bounces ≥1.0 ng/ml are rare after brachytherapy with or without neoadjuvant AD, occurring in less than 10% of patients. Low PBs have little impact on BF, but as PB amplitude increases, the BF rate increases. BF definitions based on AN are less sensitive to PB after brachytherapy. Published by Elsevier Inc. on behalf of American Brachytherapy Society.

Keywords: PSA bounce; Biochemical failure; Brachytherapy; Androgen deprivation

Introduction

The posttreatment prostate specific antigen (PSA) profile is the most consistently used modality for assessing the efficacy of prostate cancer treatment. Biochemical failure (BF) because of a rising PSA is the initial hallmark of disease progression before the clinical manifestation of a local recurrence or distant metastasis. It is with this benchmark that second-line therapy is initiated in attempt to prevent the eventual dissemination of disease. Because of the dependence on the PSA profile for judging treatment success, fluctuations or bounces in PSA can cause considerable anxiety for both patients and physicians. Differentiating benign fluctuations from failure is paramount in this setting, preventing the unnecessary administration of potentially toxic salvage therapies.

PSA bounce (PB) is a well-known physiologic phenomenon after irradiation of the prostate, first described in the postbrachytherapy setting (1, 2). PB generally occurs within the first 2 years after implantation, with a median time of onset ranging from 13 months (3) to 2.2 years (4). Although precipitating factors, such as bacterial/radiation prostatitis,

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* Corresponding author. Department of Radiation Oncology, Beaumont Cancer Institute, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, MI 48073. Tel.: +1-248-551-2080; fax: +1-248-551-0089.

E-mail address: lkestin@beaumont.edu (L.L. Kestin).

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ejaculation, instrumentation of the genitourinary tract, laboratory error, and bicycle riding have been identified (2, 4–6), most of the elevations remain idiopathic in nature. Associations with younger age (7–15), glandular volume (8), and implant dose (8–10) have been reported after interstitial implantation as monotherapy or in combination with external beam radiation therapy (EBRT).

A universally accepted definition of PB has yet to be established. A myriad of definitions have been used to measure bounce frequency, including rises of 0.1 (3, 7–9), 0.2 (10, 11, 14–16), 0.4 (8, 9, 17–20), and 0.5 ng/ml (21), as well as rises of 15% (4) and 35% (8, 22) of the prior PSA level. In some studies, PB analyses have been limited to PB over a specific number of PSA measurements or within a specified period of time. Although many series have required the PSA level to return to the prebounce baseline to classify a case as a bounce, some studies have only required a decrease of any level after an increase. Not surprisingly, the rates of PB in the published literature are reflective of the varying sensitivities of the PB definitions used and range from 17% to 62% in those receiving brachytherapy (4, 8).

The purpose of this study was to assess the clinical and biochemical impact of PB on a population of patients treated with brachytherapy modalities. Rather than use a predetermined cutpoint for PB, the population was examined using a spectrum of bounce definitions. We included a heterogeneous population of patients treated with either low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy as monotherapy, or HDR brachytherapy combined with EBRT (HDR boost). The patients receiving androgen deprivation (AD) were included. Finally, to analyze the relationships of PB with different BF definitions, three BF definitions and two definitions for PSA nadir were applied for this study.

Methods and materials

Patient population

From 1987 to 2003, 691 patients with clinically localized (T1–T3N0M0) prostate cancer were treated with brachytherapy at William Beaumont Hospital. All the patients had biopsy-proven adenocarcinoma of the prostate and underwent brachytherapy with curative intent either as monotherapy or in combination with EBRT. Pretreatment PSA levels were available for all the patients and posttherapy PSA levels were prospectively followed with measurements drawn in 3–6-month intervals at the discretion of the treating physicians. For all the patients, routine serial posttreatment PSA levels were obtained at the same institution. Before May of 1996, the Tandem-R monoclonal method (Hybridtech, Inc., San Diego, CA) was used to assess serum PSA. Normal values with this method ranged from <0.4 to 4.0 ng/ml with the lower limit of detection at 0.4 ng/ml. In May of 1996, the Tandem-R monoclonal method was replaced with the Abbott microparticle immunoassay (IMX, Abbott Laboratories, Chicago, IL). This assay allowed for an improved detection sensitivity of 0.1 ng/ml with a resultant normal range from <0.1 to 4.0 ng/ml.

Treatment

Low-risk patients receiving brachytherapy as monotherapy underwent a transperineal interstitial implant under ultrasound guidance with either LDR permanent ^{103}Pd seeds to a dose of 120 Gy ($n = 191$) or HDR brachytherapy to a dose of 38 Gy delivered in four fractions of 9.5 Gy using an ^{192}Ir source ($n = 93$). Intermediate- and high-risk patients receiving HDR boost ($n = 407$) were treated with a technique that has been previously published (23). Briefly, the patients were treated to the pelvis using 10- or 18-MV photons in a four-field beam arrangement to deliver a median dose of 46.0 Gy in 1.8–2.0-Gy fractions. Two or three HDR implants were integrated during the EBRT phase with dose escalating from 5.5 to 11.5 Gy per implant over the course of the trial. A total of 317 patients (46%) received AD, primarily as a neoadjuvant treatment modality for cytoreduction. AD consisted of 3–6 months of a gonadotropin-releasing hormone analogue ± an antiandrogen with reevaluation at 3-month intervals.

PB and nadir definition

The PB was defined as any increase in PSA level followed by a spontaneous decrease at any future point in time to the prebounce level or lower. The PSA values after salvage therapy (i.e., AD) were ignored. Multiple bounce amplitudes were analyzed in our population to assess the impact of various magnitudes of PB. The lowest definition of PB in this study was a rise of ⩾0.1 ng/ml. Incremental analyses in gradations of 0.1 ng/ml were then performed for the patient population of up to 1.0 ng/ml, after which gradations of 1.0 ng/ml were analyzed. The PSA nadir was defined using two methods, applying both the current nadir (CN) and absolute nadir (AN) concepts. A prospective definition termed CN is the lowest PSA measurement before any current PSA measurement. It is the definition most often used in every day clinical situations. The AN is the lowest PSA measurement during the entire followup period. The latter allows for the analysis of the entire PSA profile during the followup period in a retrospective manner.

BF and clinical failure endpoints

Three BF definitions were applied for this analysis: (*1*) three consecutive rises after reaching the PSA nadir according to the ASTRO Consensus Panel statement (“3 rises”) (24); (*2*) any increase to ⩾2 ng/ml above the nadir value (“nadir + 2” or the Phoenix definition) (25); (*3*) a threshold cutoff of ⩾3.0 ng/ml at or after nadir (“threshold 3”).