THE JOURNAL OF
SEXUAL MEDICINE

External Beam Radiotherapy Affects Serum Testosterone in Patients With Localized Prostate Cancer

Raisa S. Pompe, MD,[1,2] Pierre I. Karakiewicz, MD,[1,3] Emanuele Zaffuto, MD,[1,4] Ariane Smith, MD,[3] Marco Bandini, MD,[1,4] Michele Marchioni, MD,[1,5] Zhe Tian,[1] Sami-Ramzi Leyh-Bannurah, MD,[1,2,6] Jonas Schiffmann, MD,[7] Guila Delouya, MD, MSc,[8] Carole Lambert, MD, MSc,[8] Jean-Paul Bahary, MD, MSc,[8] Marie Claude Beauchemin, MD,[8] Maroie Barkati, MD,[8] Cynthia Ménard, MD,[8] Markus Graefen, MD,[2] Fred Saad, MD,[1,3] Derya Tilki, MD,[2,6] and Daniel Taussky, MD[8]

ABSTRACT

Background: Previous studies have examined testosterone levels after external beam radiation (EBRT) monotherapy, but since 2002 only sparse contemporary data have been reported.

Aim: To examine testosterone kinetics in a large series of contemporary patients after EBRT.

Methods: The study was conducted in 425 patients who underwent definitive EBRT for localized prostate cancer from 2002 through 2014. Patients were enrolled in several phase II and III trials. Exclusion criteria were neoadjuvant or adjuvant androgen-deprivation therapy or missing data. Testosterone was recorded at baseline and then according to each study protocol (not mandatory in all protocols). Statistical analyses consisted of means and proportions, Kaplan-Meier plots, and logistic and Cox regression analyses.

Outcomes: Testosterone kinetics after EBRT monotherapy and their influence on biochemical recurrence.

Results: Median follow-up of 248 assessable patients was 72 months. One hundred eighty-six patients (75.0%) showed a decrease in testosterone. Median time to first decrease was 6.4 months. Median percentage of decrease to the nadir was 30% and 112 (45.2%) developed biochemical hypogonadism (serum testosterone < 8 nmol/L). Of all patients with testosterone decrease, 117 (62.9%) recovered to at least 90% of baseline levels. Advanced age, increased body mass index, higher baseline testosterone level, and lower nadir level were associated with a lower chance of testosterone recovery. Subgroup analyses of 166 patients treated with intensity-modulated radiotherapy confirmed the results recorded for the entire cohort. In survival analyses, neither testosterone decrease nor recovery was predictive for biochemical recurrence.

Clinical Implications: EBRT monotherapy influences testosterone kinetics, and although most patients will recover, approximately 45% will have biochemical hypogonadism.

Strengths and Limitations: We report on the largest contemporary series of patients treated with EBRT monotherapy in whom testosterone kinetics were ascertained. Limitations are that testosterone follow-up was not uniform and the study lacked information on health-related quality-of-life data.

Conclusion: Our findings indicate that up to 75% of patients will have a profound testosterone decrease, with up to a 40% increase in rates of biochemical hypogonadism, although the latter events will leave biochemical recurrence unaffected. **Pompe RS, Karakrewicz PI, Zaffuto E, et al. External Beam Radiotherapy Affects Serum Testosterone in Patients With Localized Prostate Cancer. J Sex Med 2017;XX:XXX–XXX.**

Received February 19, 2017. Accepted April 30, 2017.

[1]Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Canada;

[2]Martini Clinic, Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;

[3]Department of Urology, University of Montreal Health Center, Montreal, Canada;

[4]Department of Urology and Division of Experimental Oncology, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy;

[5]Department of Urology, SS Annunziata Hospital, G.D. Annunzio University of Chieti, Chieti, Italy;

[6]Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany;

[7]Department of Urology, Academic Hospital Braunschweig, Braunschweig, Germany;

[8]Department of Radiation Oncology, University of Montreal Health Center, Montreal, Canada

http://dx.doi.org/10.1016/j.jsxm.2017.04.675

Key Words: Testosterone Recovery; Biochemical Recurrence; External Beam Radiation; Testosterone; Testosterone Kinetics; Biochemical Hypogonadism

INTRODUCTION

Several studies have described the phenomenon of testosterone decrease after radical prostatectomy (RP) or radiotherapy (RT) monotherapy in patients with localized prostate cancer (PCa).[1–3] One of the largest series was published in 2002 by Pickles and Graham[1] and analyzed data obtained from 666 men who underwent external beam RT (EBRT) without androgen-deprivation therapy. That study reported a median testosterone decrease of 17% from baseline testosterone (BST). Testosterone did not affect rates of biochemical recurrence (BCR). Since this landmark study, only smaller-scale series have examined this phenomenon in contemporary patients after RT and reported conflicting results.[4–7]. Based on the divergence of findings the aim of the present study was to examine testosterone kinetics after definitive EBRT in a larger series of contemporary patients with PCa. We hypothesized that decreases in serum testosterone and their duration might be less significant in contemporary patients than in their historic counterparts.

METHODS

Study Population

This study relied on data of 425 patients who underwent definitive EBRT (three-dimensional conformal or IMRT) for localized PCa from 2002 through 2014 at our institution within the scope of several prospective registered phase II and III trials. Since 2007, all patients have received IMRT. Patients with neo- or adjuvant androgen-deprivation therapy (n = 146) and those with missing data on outcome variables (n = 31) were excluded, resulting in 248 assessable patients. Before treatment, all patients underwent clinical examination and diagnostic assessment including pretreatment prostate-specific antigen (PSA) and serum BST testing. Follow-up testosterone levels were measured according to the respective study protocols and expressed as the ratio of BST. Testosterone follow-up was not mandatory in all study protocols, which accounts for the large number of missing data. None of the patients received testis protection during RT. Biochemical hypogonadism was defined according to the European Association of Urology guidelines on male hypogonadism as a serum testosterone level lower than 8 nmol/L.[8] Primary outcomes were testosterone decrease and recovery to at least 90% of BST.[9] In addition, possible risk factors for testosterone decrease and recovery, such as age, body mass index (BMI), total EBRT dose, BST, and percentage of decrease at the nadir, were analyzed. The association between testosterone decrease vs recovery and BCR was examined. BCR was defined according to the Phoenix criteria as a PSA level of at least 2 ng/mL above the post-EBRT nadir and BCR-free survival was calculated from last day of EBRT to the date of the registered BCR or last follow-up visit, whichever came first.[10] Confirmatory subgroup analyses were performed in patients who were treated with IMRT from 2007 through 2014.

Statistical Analysis

Descriptive statistics used means and proportions. Uni- and multivariable logistic regression analyses tested the impact of risk variables on testosterone decrease and recovery. For survival analyses, the Kaplan-Meier method and log-rank test for comparison of survival between groups were used.[11] Cox multivariable regression analyses tested the effect of testosterone decrease and recovery on BCR. All analyses were adjusted for age, biopsy Gleason score, clinical tumor stage, and preoperative PSA. All statistical tests were two-sided with a level of significance set at a P less than .05. Analyses were performed using R 3.3.0 software.

RESULTS

Table 1 presents demographic and disease characteristics of all 248 assessable patients and of 166 patients after IMRT. Median age was 71 years (interquartile range [IQR] = 65–74) and median BST was 10.1 nmol/L (IQR = 8.4–12.7). Low BST (<8 nmol/L) was found in 12 patients and no patient had high BST values (≥35 nmol/L). Most had a biopsy Gleason score of 7 (76.2%) and a clinical tumor stage of cT1 (57.7%). Median oncologic follow-up was 72 months (IQR = 52–102) and median testosterone follow-up was 69 months (IQR = 46.2–91.2). A median of 9 testosterone measurements (IQR = 6–14) was obtained during follow-up.

Testosterone Decrease

Testosterone decreases from BST were recorded in most men: 186 (75.0%) had any decrease, 162 (65.3%) had at least 10% decrease, 111 (44.8%) had at least 25% decrease, 33 (13.3%) had at least 50% decrease, and 3 (1.2%) had at least 90 decrease. Of all 248 patients, 62 (25%) did not show a testosterone decrease. Median time to first testosterone decrease was 6.4 months (IQR = 2.5–15.7; Figure 1). Median percentage of decrease from BST to the nadir level was 30% (IQR = 17.1–45.1). Moreover, median absolute decrease was 3.3 nmol/L (IQR = 1.6–5.2) and resulted in a median testosterone level of 7.3 nmol/L (IQR = 5.5–8.9) at the nadir. Testosterone levels no higher than 8 nmol/L (biochemical hypogonadism) were recorded in 112 patients (45.2%). Of note, 12 patients (4.9%) had biochemical hypogonadism at baseline.