Testosterone Therapy after Radiation Therapy for Low, Intermediate and High Risk Prostate Cancer

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Purpose: Limited literature exists regarding the safety of testosterone therapy in men treated for prostate cancer. We present multi-institutional data on testosterone therapy in hypogonadal men with prostate cancer treated with radiation therapy.

Materials and Methods: We retrospectively reviewed the records of hypogonadal men treated with testosterone therapy after radiation therapy for prostate cancer at 4 institutions. Serum testosterone, free testosterone, estradiol, sex hormone-binding globulin, prostate specific antigen, prostate specific antigen velocity and prostate biopsy findings were analyzed.

Results: A total of 98 men were treated with radiation therapy. Median age was 70.0 years (range 63.0 to 74.3) at initiation of testosterone therapy. Median baseline testosterone was 209 ng/dl (range 152 to 263) and median baseline prostate specific antigen was 0.08 ng/ml (range 0.00 to 0.33). In the cohort the tumor Gleason score was 5 in 3 men (3.1%), 6 in 44 (44.9%), 7 in 28 (28.6%), 8 in 7 (7.1%) and 9 in 4 (4.1%). Median followup was 40.8 months (range 1.5 to 147). Serum testosterone increased to a median of 420 ng/dl (range 231 to 711) during followup ($p < 0.001$). Overall a nonsignificant increase in mean prostate specific antigen was observed from 0.08 ng/ml at baseline to 0.09 ng/ml ($p = 0.05$). Among patients at high risk prostate specific antigen increased from 0.10 to 0.36 ng/ml ($p = 0.018$). Six men (6.1%) met criteria for biochemical recurrence.

Conclusions: Testosterone therapy in men following radiation therapy for prostate cancer was associated with a minor increase in serum prostate specific antigen and a low rate of biochemical recurrence.

Abbreviations and Acronyms

ADT = androgen deprivation therapy
BCR = biochemical recurrence
CaP = prostate cancer
EBRT = external beam RT
FT = free T
GI = Gleason score
PIN = prostatic intraepithelial neoplasia
PSA = prostate specific antigen
PSAV = PSA velocity
RP = radical prostatectomy
RT = radiation therapy
T = testosterone
TTh = T therapy

Key Words: prostatic neoplasms, prostatectomy, testosterone, hormone replacement therapy, radiotherapy

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HYPOGONADISM, which is diagnosed in approximately 500,000 men annually in the United States, shows an increasing incidence with age and is characterized by low serum T and symptoms including loss of libido, erectile dysfunction, depression, lethargy, concentration difficulties, sleep disturbances, osteoporosis and loss of muscle mass.[1] TTh ameliorates these symptoms in most men. Hypogonadism most commonly affects middle-aged or older men, a population that is also frequently affected by CaP. Thus, these conditions often coexist, especially as RT for CaP is associated with lower serum T.[2] However, TTh has historically been contraindicated in men with CaP due to concern that higher serum T would enhance CaP growth.[3]

Recent clinical experiences have suggested that TTh is not as risky as once believed in men with CaP. In multiple series in which TTh was offered to men following RP 4 CaP recurrences were observed among 177 cases.[4–7] However, the safety of TTh in men after RT for CaP is more uncertain, in part due to the small number of reported cases. Furthermore, TTh in men with CaP following RT may appear more risky than after RP, in part due to the chance of residual CaP after RT, the unknown status of lymph nodes or surgical margins and absent pathology data on the entire prostate gland. However, several small studies in a total of 69 patients with CaP treated with TTh following brachytherapy and/or EBRT have revealed transient increases in PSA but no CaP recurrence or progression.[8–11] In addition, in men with CaP on active surveillance no significant increases in PSA or CaP progression have been observed.[12]

We present our multi-institutional experience of the effects of TTh on longitudinal CaP outcomes in hypogonadal men after RT.

MATERIALS AND METHODS

Patient Identification and Data Acquisition

We retrospectively reviewed the records of men with hypogonadism treated with TTh after RT for CaP at a total of 4 institutions, including Baylor College of Medicine, Men's Health Boston, University of South Florida, and South Texas Urology and Urologic Oncology. Institutional review board approval was obtained from all participating institutions and data sharing agreements were put in place. RT encompassed EBRT and brachytherapy with men in the cohort undergoing EBRT and/or brachytherapy. Patients underwent RT for CaP from 1994 to 2012 and received TTh between 1999 and 2013. Men were diagnosed with hypogonadism by hypogonadal symptoms, including low libido, erectile dysfunction and fatigue, as well as by biochemical findings, including serum T 350 ng/dl or less, and/or FT less than 1.5 ng/dl or calculated FT less than 100 pg/ml. Patients received TTh via gel, injection or subcutaneously implanted pellets.

Baseline serum T, FT, estradiol, sex-hormone binding globulin and PSA were determined before TTh initiation. Followup serum hormone values were evaluated every 3 to 6 months thereafter. All followup serum values presented correspond to the most recent value available. Followup represents the time from initial presentation through the most recent followup. Laboratory testing was performed at the Laboratory for Male Reproductive Research and Testing, Baylor College of Medicine (LIL and MK); Tosoh Bioscience, San Francisco, California (AM); LabCorp, Burlington, North Carolina (MFS); or Quest Diagnostics, Madison, New Jersey (AM and RC).

Men were grouped into risk subgroups, including low—Gl 6 or less, intermediate—Gl 3 + 4 and 4 + 3, and high—Gl 8 or greater. BCR was deemed to have occurred if any of certain conditions were met, including 1) PSA greater than absolute nadir plus 2 ng/ml, 2) PSA greater than current nadir plus 3 ng/ml or 3) 2 consecutive increases in PSA of 0.5 ng/ml or greater.[13] Current nadir was defined as the lowest PSA before the elevated PSA concerning for BCR. Absolute nadir referred to the lowest PSA during followup.

Statistical Analysis

Baseline and followup serum values were compared using the Wilcoxon signed rank test. PSAV was calculated by linear regression using at least 3 PSA values during 12 months or greater. PSAV was compared across subgroups with the Kruskal-Wallis and Fisher exact tests. All analyses were performed using SPSS®, version 21 with $p \leq 0.05$ considered significant.

RESULTS

We identified 98 hypogonadal men with a history of CaP who underwent RT and were subsequently started on TTh (supplementary table 1, http://jurology.com/). Median age was 70.0 years (range 34 to 85). Of the men 50 (51%) received ADT in addition to RT for initial CaP management while the remainder received RT alone. The interval between ADT cessation and TTh initiation was 5 to 60 months. No individual was receiving ADT at the time of TTh initiation.

Initial prostate biopsy data were available on 86 men (87.8%), including 3 (3.1%) with Gl 5, 44 (44.9%) with Gl 6, 28 (28.6%) with Gl 7, 7 (7.1%) with Gl 8 and 4 (4.1%) with Gl 9 disease. TTh was started a median of 28.6 months (range 13.8 to 40.4) after RT. The mode of TTh was gels in 65%, injections in 24% and pellets in 11%. The median time from TTh initiation to the most recent followup visit was 40.8 months (range 1.5 to 147).

Table 1 lists baseline and followup results. Median serum T increased from 209 to 420 ng/dl ($p < 0.001$) and median free T increased from 5.9 to 10.7 pg/ml ($p = 0.001$) at followup. Median serum PSA was 0.08 ng/ml at baseline and 0.09 ng/ml at followup ($p = 0.05$). Serum estradiol and sex-hormone binding globulin did not change significantly.