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Review

# Current state of practice regarding testosterone supplementation therapy in men with prostate cancer

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ABSTRACT

Hypogonadal men are characterized by low serum testosterone and symptoms of low energy, decreased libido, and muscle mass as well as impaired concentration and sexual functioning. Men with prostate cancer (PCa) currently on active surveillance or post-therapy, have traditionally been excluded from management paradigms given the decade-old concern that testosterone caused PCa growth. However, there appears to be little or no relationship between serum testosterone concentration and PCa. Androgen action in the prostate has long been known to be affected by the kinetics of receptor saturation and, as such, testosterone beyond a certain baseline is unable to stimulate prostatic growth due to complete intra-prostatic androgen receptor binding. Given this physiologic concept, many clinical investigators have begun to promote testosterone supplementation therapy (TST) as safe in men with PCa. This review examines the basics of testosterone physiology and summarizes the most recent findings on the use of TST in men with PCa on active surveillance and following treatment with external beam radiotherapy, brachytherapy and radical prostatectomy.



**Contents**



## 1. Introduction

Hypogonadism is increasingly becoming a recognized clinical condition in men of all ages. Testosterone levels decrease by ~1% per year beginning at the age of 30 years [1], and it is estimated that ~7% of men aged 30–69 years, and 18% of men greater than 70 years old, are currently experiencing symptoms of hypogonadism [2]. Treatment primarily involves supplementation with exogenous testosterone via numerous formulations including topical gels or liquids, injectables and implantable pellets [3,4]. Indeed, testosterone supplementation therapy (TST) is currently one of the most commonly prescribed pharmaceutical regiments in the world with administration producing improvements in hypogonadal symptoms such as decreased energy, libido, muscle mass, and bone density [5,6].

*Abbreviations:* TST, testosterone supplementation therapy; CaP, prostate cancer; DHT, 5α-dihydrotestosterone; PSA, prostate specific antigen.

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**Table 1**
A summary of the available studies that have used TST in men with previously diagnosed PCa.

| Author | Year | Study design | Patient # | Type of tx | Results |
|---|---|---|---|---|---|
| Calof et al. | 2005 | Meta-Analysis | 644 | TST in men with no hx of PCa | Rates of PCa, PSA >4 ng/ml, and biopsies were higher in the TST group than in placebo although differences between the groups were not statistically significant. Higher incidence of hematocrit >50% in TST group. The frequency of CV events, sleep apnea or death was not significantly different between the two groups. |
| Shabsigh et al. | 2009 | Systematic Review | 2292 | Various | No studies demonstrated that TST increased PCa risk or increased Gleason grade in treated vs untreated men. TST did not have a consistent effect on PSA. |
| Morgentaler et al. | 2011 | Retrospective case series | 13 | TST in men with untreated Pca | Mean serum total testosterone increased from 238 to 664 with no significant change in PSA or prostate volume. Biopsies in 2 men suggested upgrading. Repeat biopsy in one man and a prostatectomy in another indicated no progression. No local progression or distant disease. |
| Morales | 2011 | Retrospective case series | 7 | TST in men with untreated Pca | Unpredictable, variable increase in PSA with TST. Interruption of TST invariably decreased PSA to pre-therapy levels. |
| Morgentaler | 2009 | Case report | 1 | TST in a man with untreated Pca | Overall decline in PSA after receiving TST for 2 years. No clinical progression of disease noted. |
| Rhoden & Morgentaler 2003 | | Retrospective case series | 75 | TST in men with and without high grade PIN | PSA similar at baseline and 12 mo after TST in men with and without PIN. One man in the PIN+ group was found to have cancer on biopsy after abnormal DRE. |
| Sarosdy | 2007 | Retrospective case study | 31 | TST in men after brachytherapy for early prostate cancer | None showed recurrence or progression of prostate cancer. PSA <1 in all patients. |
| Morales et al. | 2009 | Prospective case study | 5 | TST in men after external beam radiotherapy | One of five patients had transitory increase in PSA after a mean follow-up of 14.5 months. None had PSA levels >1.5 ng/ml. Mean serum testosterone and improvement in hypgonadal symptoms increased significantly. |
| Pastuszak et al. | 2013 | Retrospective case series | 13 | TST after radiation therapy for Pca | At median follow-up of 29.7 months after initiating TST, a significant increase in mean testosterone and SHBG with no significant increases in hemoglobin hematocrit PSA. No significant increases in PSA or cancer recurrences observed at any follow-up interval |
| Pastuszak et al. | 2013 | Retrospective case series | 103 | TST in men after radical prostatectomy | At median follow-up of 27.5 months, significant increases in testosterone and PSA in both high risk and non-high risk prostate cancer groups. Referrals to radiation oncology or subsequent salvage therapy more frequent in reference control group. Significantly increased number of T3b tumors in reference group vs TST group. |
| Agarwal & Oefelein | 2005 | Retrospective case series | 10 | TST in men after radical prostatectomy | At median followup of 19 months, all patients had PSA <0.1 with statistically significant improvements in serum testosterone and hypogonadal symptoms. |
| Kaufman & Graydon | 2004 | Retrospective case series | 7 | TST in men after radical prostatectomy | No biochemical or clinical evidence of cancer recurrence. PSA remained <0.1 in all patients. |
| Khera & Lipshultz | 2009 | Retrospective case series | 57 | TS\T in men after radical prostatectomy | After a mean follow up of 13 months after initiation of TST after radical prostatectomy, no increases in PSA values were noted. |

Historically, significant concerns have been raised regarding the use of TST in hypogonadal patients who are elderly [7], have cardiovascular disease [8] as well as active or treated (either with radiation or surgery) prostate cancer (PCa) [9,10]. This concern was founded upon previous clinical observations that PCa was androgen dependent and that androgen deprivation resulted in the regression of PCa with a concurrent decrease in prostate specific antigen (PSA) [11–13]. As such, traditional teaching declared that a history of PCa was an absolute contraindication for the use of any type of TST. For example, Fowler and Whitmore [14] conducted an early retrospective review focused on the response of 67 patients with metastatic prostatic adenocarcinoma to the administration of exogenous testosterone. The majority of the men exhibited unfavorable responses that regressed following removal of the TST [14].

Recent work is disputing these concepts [9,10,15]. A recent manuscript by Feneley and Carruthers [16] highlighted the results of a recent audit examining the incidence of PCa during long-term TST conducted from the UK Androgen Study. A total of 1365 men aged 28–87 years with hypogonadism were followed for up to 20 years with a total of 14 new cases of PCa diagnosed at a rate of one case per 212 years of treatment [16]. All tumors were localized and suitable for curative treatment with the PCa rate during long-term TST equivalent to that of the general population [16]. Given that PCa is the most commonly diagnosed malignancy in men after skin cancer with >200,000 new cases diagnosed yearly [17], and the increasing trend toward active surveillance in PCa, an understanding of the current TST literature is essential (Table 1). This review highlights the basic physiology underlying testosterone action in men and summarizes the current state of practice regarding TST in men with PCa who are currently on active surveillance or have undergone treatment with radiotherapy, brachytherapy or radical prostatectomy.

## 2. Physiology of testosterone and the role of androgens in the prostate

In 1941, Huggins and Hodges first demonstrated, in a case series of 3 patients, that PCa regression occurred following orchiectomy [13,18]. This and the associated series of landmark studies [11–13,18] formed the basis of the current standard of care in the treatment of metastatic PCa. By implying a direct correlation between serum testosterone levels and PCa, the premise was simple; a lower testosterone resulted in PCa regression and vice versa. Later *in vitro* and clinical work suggested that administration of exogenous testosterone stimulated growth of prostatic adenocarcinoma cells [14,19]. These concepts then formed the foundation for the clinical mantra that exogenous TST should be avoided in men with PCa [20–22].

Testosterone, the principal circulating androgen in men, is predominantly synthesized by testicular Leydig cells (90%) under the control of Luteinizing hormone (LH) released from the pituitary [23]. The remainder (10%) originates from the adrenal glands [24]. Primarily derived from 27-carbon cholesterol, an enzymatic pathway alters the framework to the 19-carbon steroids that are traditionally known as androgens [25]. The bioavailable, or