SEXUAL MEDICINE REVIEWS REVIEW

# Testosterone Therapy After Prostate Cancer Treatment: A Review of Literature

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## ABSTRACT

**Introduction:** Although testosterone therapy (TTh) is the standard practice in otherwise healthy hypogonadal men, this therapy has historically been contraindicated in men with a history of prostate cancer. Recent evidence suggests that there is minimal or no prostate cancer growth in the setting of TTh administration in men definitively treated for non-metastatic prostate cancer.

**Objective:** To review the evidence supporting the safety and efficacy of TTh in patients previously treated for localized prostate cancer.

**Methods:** A literature review of the PubMed database was performed to identify studies evaluating the safety and efficacy of TTh in patients with a history of prostate cancer. Search terms included Testosterone Therapy, Testosterone Replacement Therapy and Radical Prostatectomy, Radiotherapy, External Beam Radiation Therapy, EBRT, Brachytherapy; Prostate Cancer and Hypogonadism, Low Testosterone; Bipolar Androgen Therapy.

**Results:** Available literature provides evidence for the safe application of TTh in patients previously treated for prostate cancer with either radical prostatectomy or radiotherapy. Furthermore, there exists evidence that severely hypogonadal levels of testosterone may lead to worse oncological outcomes. More recent research has begun to elucidate the effectiveness of bipolar androgen deprivation therapy in the treatment of prostate cancer. This mechanism of action increases the level of evidence indicating that the traditional management of maintaining testosterone levels at low levels may no longer be standard of care. TTh likely has a role in improved erectile function and other quality-of-life concerns in patients developing testosterone deficiency after being treated for prostate cancer.

**Conclusions:** TTh should be offered to select hypogonadal patients who have a history of definitively treated prostate cancer. Adequately designed randomized controlled trials are necessary to confirm the safety and efficacy of TTh in this population. **Natale C, Carlos C, Hong J, et al. Testosterone Replacement Therapy After Prostate Cancer Treatment: A Review of Literature. Sex Med Rev 2021; XX:XXX–XXX.**



**Key Words:** Hypogonadism; Prostate Cancer; Radical Prostatectomy; Testosterone Therapy; Radiotherapy; Androgen Deprivation Therapy

## INTRODUCTION

Testosterone deficiency is a clinical syndrome that can include diminished libido, osteoporosis, and cognitive impairment, which results from a deficiency in the production of testosterone.[1] Although testosterone therapy (TTh) is the standard practice in otherwise healthy hypogonadal men, a history of prostate cancer was previously considered a contraindication to TTh.[2] Restriction of TTh from men with prostate cancer was largely practiced because of historical tradition.[3] The prevalence of evidence confirming that TTh benefitted quality of life led to a paradigm shift in the treatment of testosterone deficiency in men with prostate cancer, as well as the manner in which exogenous androgens affect the prostate.[3]

Since the early 1950s, testosterone was thought to cause prostate cancer or, if the man had prostate cancer, to result in increased growth of cancer. In 1941 Huggins and Hodges established the hormonal responsiveness of prostate cancer. Huggins would later go on to receive the Nobel Prize for his research on androgens and prostate cancer. They reported that the marked reductions in testosterone by castration or estrogen treatment caused metastatic prostate cancer to regress, and also

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that administration of exogenous testosterone caused prostate cancer to grow.[4] To this day, androgen ablation remains a mainstay of treatment for advanced prostate cancer.[5]

In response to literature describing no prostate cancer growth or progression in men receiving TTh, the validity of the androgen-responsiveness model was called into question.[6] On review of previous literature, Morgentaler and Traish found that reports of testosterone causing rapid growth of prostate cancer occurred in men who already had extremely low testosterone levels due to castration or estrogen treatment.[7] They concluded that the maximal androgenic stimulation of prostate tissue was reached at relatively low concentrations. This is known as the saturation model. Marks et al further described that raising serum testosterone levels did not raise testosterone levels within the prostate.[8] Experimental studies report that the concentration at which this saturation occurs is quite low.[9] Reports of men treated with TTh after treatment for localized prostate cancer have shown low to absent recurrence rates[2]; however, concern remains among practitioners that testosterone may promote recurrence.[1]

This review aims to investigate the safety and efficacy of TTh after definitive treatment for prostate cancer by evaluation of existing literature.

## METHODS

A literature review of the PubMed database was performed to identify studies evaluating the safety and efficacy of TTh in patients with a history of prostate cancer. Search terms included Testosterone Replacement Therapy and Radical Prostatectomy, Radiotherapy, External Beam Radiation Therapy (EBRT), Brachytherapy; Prostate Cancer and Hypogonadism, Low Testosterone; Bipolar Androgen Therapy.

## RESULTS

### Evidence synthesis for this review

#### Treatment of Testosterone Deficiency With TTh After Radical Prostatectomy

Radical prostatectomy (RP) is an established and standard treatment option for intermediate- and high-risk localized prostate cancer and may be offered to select low-risk localized prostate cancer patients with a high probability of progression on active surveillance.[10,11] Historically, clinicians have been hesitant to utilize TTh after RP, believing that TTh could promote recurrence or progression of prostate cancer because of increased androgen levels.[12] However, in 2004, this paradigm began to change after Kaufman and Graydon reported 7 men treated with TTh after curative RP without biochemical recurrence,[13] followed in 2005 by Agarwal and Oefelein reporting 10 patients treated with TTh for symptomatic testosterone deficiency with no biochemical recurrence at mean follow-up of 19 months.[14] Currently, the American Urological Association (AUA) guidelines state that patients who have undergone RP with favorable pathology (eg, negative margins, negative seminal vesicles, negative lymph nodes) and undetectable PSA values postoperatively can be considered for TTh.[15] However, the data supporting this statement are limited. The European Association of Urology (EAU) similarly advises TTh in symptomatic men treated surgically for localized prostate cancer while stipulating that this recommendation be limited to those with at least 1 year of follow-up and with low risk of recurrence (eg, Gleason score $< 8$, pathological stage pT1-2, preoperative PSA $< 10$ ng/mL).[16]

A review of the literature reveals several studies that demonstrate improved serum testosterone levels in patients being treated with TTh, despite a history of prostate cancer treated with RP, and without concurrent rise in clinical or biochemical recurrence in prostate cancer (Table 1). In total, 852 patients were included in this analysis,[14,15,17–28] with 24 patients showing biochemical recurrence for an overall recurrence rate of 2.8%. Despite variable lengths of follow-up, low rates of recurrence persisted. Notably, in studies that included control or reference groups, recurrence rates remained lowest in the TTh groups.[23,24,29] These data suggest that TTh therapy does not increase the rate of recurrence at or before 3.4 years of follow-up, in accordance with previous literature.[20,29–31] Cautious use of TTh in selected patients with history of prostate cancer treated with RP is warranted.

The studies included in this analysis are limited. Only one study is not limited by retrospective design[16] and only 3 include control groups.[23,24,29] In addition, the studies were not standardized in time to TTh application after RP or method of TTh application. Future randomized control trials, as well as longer follow-up studies, are needed to elucidate the safety and efficacy of TTh in patients with a history of prostate cancer treated with RP.

#### Treatment of Testosterone Deficiency With TTh After Radiotherapy

Patients who require non-conservative treatment of prostate cancer can choose either surgical management or radiotherapy. With limited randomized controlled trials available to guide further treatment, patients often determine which treatment methodology to pursue based on the recommendation of their doctors and considering their own preferences. Some studies have indicated that radiotherapy may be associated with an increased risk of mortality compared with RP.[32] Furthermore, radiotherapy may include an increased risk of residual prostate cancer, which raises additional concerns for practitioners prescribing TTh.

In 2013, Pastuzak et al retrospectively reviewed TTh treatment in 13 men who had undergone radiation therapy for the treatment of prostate cancer.[33] Of these patients, 4 had a Gleason score of 6, 7 had a Gleason score of 7, and 2 had a Gleason score of 8. Mean follow-up was 27.5 months. Despite a significant increase in mean testosterone, there was not an

observed increase in hemoglobin, hematocrit, free testosterone, estrogen or PSA, or any incidences of biochemical recurrence. Biochemical recurrence was defined as PSA greater than current nadir plus 3 ng/mL and 2 consecutive PSA increases of >0.5 ng/mL. The authors concluded that TTh in the setting of prostate cancer after radiation leads to improved hypogonadal symptoms without evidence of cancer recurrence or progression, regardless of Gleason score, although this study was limited by a small sample size. In a subsequent retrospective study, Pastuzak et al identified 98 men who had been treated with radiation therapy and then received TTh.[34] In this cohort, the Gleason scores were 5 in 3 men (3.1%), 6 in 44 men (44.9%), 7 in 28 men (28.6%), 8 in 7 men (7.1%), and 9 in 4 men (4.1%). This study demonstrated a nonsignificant increase in mean PSA (0.08 ng/ml at the baseline to 0.09 ng/ml ($P = .05$)). Among patients at high risk, prostate-specific antigen increased from 0.10 to 0.36 ng/ml ($P = .018$). There was a low rate of biochemical recurrence at 6.1% of the patients (PSA = 2.2-5.3). Notably, this study included men with history of androgen deprivation therapy (ADT) or with ADT therapy status. In patients receiving TTh previously on ADT, a rise in PSA might be expected without necessarily representing biochemical recurrence, in accordance with the saturation model. In this multi-institutional study, recurrence was defined as either PSA greater than absolute nadir plus 2 ng/ml, PSA greater than current nadir plus 3 ng/ml or 2 consecutive increases in PSA of 0.5 ng/ml or greater. Mode of treatments, namely either EBRT, brachytherapy or combined, did not show significant differences in mean PSA or PSA velocity. TTh in men after radiation therapy for prostate cancer was associated with a minor increase in serum PSA and a low rate of biochemical recurrence. This study was the largest study at that time to assess TTh after radiation therapy and served to support the growing body of evidence in favor of TTh.

A retrospective chart review conducted by Kacker et al identified 135 men who began TTh after localized prostate cancer treatment.[25] Forty of these men had been treated with either brachytherapy or EBRT, and the patients were followed up for an average of 26.7 months. Gleason scores were not noted. Of these patients, 6.7% underwent TTh after known biochemical recurrence.[25] The authors found that this group of patients did not appear to have higher rates of cancer progression than what would be expected. Of note, a large majority of these men elected to discontinue TTh because of non—cancer-related reasons, such as lack of efficacy.

**Treatment of Testosterone Deficiency With TTh After Brachytherapy.** Brachytherapy is a treatment for prostate cancer that involves introducing a radioactive source into or near the tissue being targeted, that is, the prostate.[35] Many men experience symptoms of testosterone deficiency after brachytherapy, including low libido, erectile dysfunction, and fatigue.[36] In 2007, Sarosdy et al proposed that TTh may be used in symptomatic patients with low serum testosterone provided they maintain close follow up. This study retrospectively reviewed 31 patients who received TTh after brachytherapy.[37] Of the 31 men, 3 were considered to have high-risk cancer (Gleason scores of 8 or 9). A transient rise in PSA was observed in one patient; however, no patients stopped TTh because of either cancer recurrence or progression. Although 5 patients discontinued TTh after a short trial period, most subjects (86.1%) continued treatment for a median of 4.5 years and for as long as 8.5 years, which is cited by the authors as a testament to improved quality of life.[37] The team suggested that baseline testosterone levels be assessed before definitive treatment to aid in future management. Sarosdy et al notes that their study is not able to fully address TTh safety after brachytherapy, and that prospective, randomized trials are needed to more fully confirm safety.[37] In a study conducted by Balbontin et al, 20 men received long-acting testosterone injections after low-dose, permanent brachytherapy with a goal of free testosterone concentrations >11.7 ng/dL. The patients' PSA and serum testosterone levels were followed up closely for an average of 2.5 years. The study found that PSA levels decreased significantly over the course of TTh, from a baseline mean of 0.7 ng/mL to 0.1 ng/mL at last follow-up ($P < .001$).[36] The study concluded that treatment with TTh after brachytherapy conveyed significant clinical benefits. Total and free testosterone levels increased during the duration of treatment, with an improvement in mean Sexual Health Inventory for Men scores from 17.8 to 22.1 after TTh ($P = .002$).[36] There were no cases of rising serum PSA, prostate cancer progression, or recurrence. Limitations included small sample size, limited duration of follow-up, retrospective nature, and lack of objective measures for symptoms of testosterone deficiency.[36]

In a case series by Kadomoto et al, 6 cases were followed up wherein patients received brachytherapy combined with adjuvant ADT by combined androgen blockade for 2 years.[38] All 6 cases involved high-risk prostate cancer, and patients with definite metastatic lesions, baseline PSA >0.2 ng/mL before starting TTh, treatment within the previous 2 years, or unstable cancer control were excluded. 5 of the 6 received EBRT after brachytherapy. Polycythemia is an adverse effect of TTh after brachytherapy that was seen in 1 of the 6 patients. The results of the study saw an improvement in the Aging Male Symptoms scale after TTh in all cases. 5 patients had transient rises in PSA that were not indicative of biochemical recurrence, and most patients saw definitive improvements in measures such as hemoglobin, triglycerides, total cholesterol, HbA1c, and BMI. These measures are notable because at this time, the perceived benefit of TTh has deemed it a viable option, despite limited understanding of risk necessary to quantify its risk-benefit ratio.[38] The AUA recommends careful counselling regarding this lack of definitive evidence and cessation of therapy 3 to 6 months after initiation in patients who achieve normalization of testosterone levels but fail to have improvements in symptoms of testosterone deficiency.[11] Further research using randomized

**Table 1.** Summary of studies assessing safety of testosterone therapy (TTh) in patients treated with radical prostatectomy (RP) for prostate cancer

| Author | Month and year | n | Study population characteristics | Study type | Definition of biological recurrence | Median follow-up (from TTh initiation) | Outcomes | Conclusions |
|---|---|---|---|---|---|---|---|---|
| Kaufman and Graydon[13] | Sept 2004 | 7 | GS were 6 (n = 6) and 7 (n = 1), one positive margin, PSA range 4.4-6.6 | Retrospective | Greater than 0.1 ng/ml PSA | Not specified | No biochemical recurrence or clinical indicators of cancer recurrence. | Cautious use of TTh in selected prostate cancer survivors is warranted. |
| Agarwal and Oefelein[14] | Nov 2005 | 10 | GS were 6 (n = 2), 7 (n = 7) and 8 (n = 1), mean PSA was 7.0 (range 5.8-12.6) | Retrospective | Greater than 0.1 ng/ml PSA | Mean: 19 months | No cases of biochemical recurrence during study. | TTh can be used in selected patients treated with RP. |
| Nabulsi et al[17] | May 2008 | 22 | GS were 6 (n = 15) and 7 (n = 7), mean PSA 5.9 ± 3.5 | Prospective | Not specified | 20 months | One patient (G8 disease) showed PSA recurrence at 17 months post-RP and 12 months on TTh. | The administration of TTh is safe at 2 years post-T administration in carefully selected patients. |
| Davila et al[18] | May 2008 | 14 | Mean GS was 6.2, mean PSA was 6.05, all negative surgical margins | Retrospective | Not specified | 12 months | No significant differences in PSA before and after starting TTh. | TTh is safe and efficacious in men after treatment of prostate cancer. |
| Khera et al[19] | April 2009 | 57 | GS were <7 (n = 24), 7 (n = 26), >7 (4), mean PSA was 5.58, all negative surgical margins | Retrospective | Detectable PSA | Mean: 13 months | No cases of biochemical recurrence during study. | TTh is effective at improving testosterone levels without increasing PSA values. |
| Sathyamoorthy et al[20] | March 2010 | 133 | 21 patients were high risk (GS ≥ 8, positive surgical margins, or positive nodal disease) | Retrospective | Greater than 0.1 ng/ml PSA | 12 months | No increases in PSA and thus no biochemical recurrence noted. | TTh effective in improving testosterone levels without increasing PSA in hypogonadal men who have undergone RP. |
| Isbarn et al[21] | Apr 2010 | 69 | All patients negative surgical margins. | Retrospective | Not specified | 19 months | No cases of biochemical recurrence during study. | TTh can be offered to select patients with history of prostate cancer. |
| Matsushita et al[22] | Apr 2012 | 61 | Mean GS was 7, mean PSA was 4.9 ± 2.6 | Retrospective | Not specified | Mean: 26 months | There was one reported case of biochemical recurrence. Significant increase in total testosterone. | TTh safe and efficacious on long-term follow-up. |

(continued)

**Table 1.** Continued

| Author | Month and year | n | Study population characteristics | Study type | Definition of biological recurrence | Median follow-up (from TTh initiation) | Outcomes | Conclusions |
|---|---|---|---|---|---|---|---|---|
| Pastuszak et al[23] | Aug 2013 | 103 | GS were <8 (n = 75), ≥8 (n = 1), unknown (n = 19), median PSA was 5.2, positive margins (n = 17), positive lymph nodes (n = 1), positive seminal vesicle (n = 3) | Retrospective | Greater than 0.2 ng/ml | 27.5 months | There were 4 reported cases of biorecurrence (4%) in men being treated with TTh and history of RP. This compared to 16.3% risk of recurrence in reference group. | TTh does not appear to increase cancer recurrence rates in men treated with RP. |
| Wynia et al[24] | Apr 2014 | 57 | Not specified | Retrospective | Not specified | 24 months | No significant difference noted in PSA levels between treatment and control group ($P = .157$); one case of biochemical recurrence in treatment group (recurrence rate = 1.8% compared to 14.8% in control group). | TTh did not increase risk of biochemical recurrence in patients previously treated with RP for prostate cancer. |
| Kacker et al[25] | Apr 2014 | 53 | Not specified | Retrospective | PSA greater than 0.2 ng/dL) | 30 months | No cases of biochemical recurrence during study. | TTh does not appear to cause higher than expected rates of prostate cancer progression in men with prostate cancer. |
| Ory et al[26] | Oct 2016 | 22 | Not specified | Retrospective | Postop PSA >0.2ug/l with a second confirmatory PSA of over 0.2 μg/l | 41 months (overall sample) | No biological recurrence noted in men being treated with TTh with history of RP. | TTh safe after definitive treatment for prostate cancer. |
| Morgentaler et al[27] | Apr 2018 | 92 | Not specified | Retrospective | Greater than 0.3 ng/ml | 19 months | Biochemical recurrence was observed in 6 cases (6.5%). | Results of long-term follow-up reassuring for clinicians considering TTh for symptomatic men with history of prostate cancer. |

(continued)

Table 1. Continued

| Author | Month and year | n | Study population characteristics | Study type | Definition of biological recurrence | Median follow-up (from TTh initiation) | Outcomes | Conclusions |
|---|---|---|---|---|---|---|---|---|
| TE Ahlering et al[28] | Mar 2020 | 152 | GS were <8 (n = 143), ≥8 (n = 9), mean PSA was 7.2 ± 5.9 | Retrospective | 2 consecutive PSAs greater than or equal to 0.2 ng/dl | Mean: 3.4 years | Biochemical recurrence seen in 11 patients (recurrence rate of 7.2% compared to 12.6% in the control group). TTh group was ~54% less likely to show biochemical recurrence compared to the control group (hazard ratio 0.54, 95% CI 0.292-0.997). | Group receiving TTh after RP showed significantly reduced biochemical recurrence and delayed time to biochemical recurrence. |

control trials is necessary to demonstrate definitive findings.[11,37,38]

Notably, the currently available research lacks consistent, concrete criteria indicating appropriate initiation of TTh in patients treated for prostate cancer with radical therapy.[38] Time to initiation of TTh, baseline PSA values, and exclusion criteria have differed widely among studies. To be classified as testosterone deficient, testosterone levels must be less than 300 ng/dL, and it is necessary that signs and symptoms of testosterone deficiency are also present.[11] This poses a challenge, attested to by the limitations proposed by Balbontin et al because the signs and symptoms of testosterone deficiency may be non-specific and cross over with other medical conditions.[11,36]

**Treatment of Testosterone Deficiency With TTh After External Beam Radiation Therapy.** EBRT, which involves the delivery of radiation externally to target tumor cells, is the most used form of radiation in locally advanced prostate cancer. It has been demonstrated to be ineffective when used alone, so combination with hormonal therapy has traditionally been observed.[39] In a study by Morales et al, 5 men with symptoms of testosterone deficiency after EBRT were treated with TTh.[40] 2 patients had Gleason scores of 6, one had a score of 7, and 2 had scores of 8. These patients were followed up for an average of 14.5 months and included an assessment of prostate health via DRE and PSA, TTh response, hematological evaluation, and lipid profiles. Side effects encountered in this study included headaches in one patient, who subsequently ceased treatment as a result. The results of the study showed no recurrence of prostate cancer, defined as PSA levels >1.5 ng/mL, during follow-up. All patients reported improvements in hypogonadal symptoms. 4 reported decreased hot flushes, decreased fatigue, and increased libido, whereas 2 subjects reported improved erectile dysfunction.[40] The authors concluded that men with testosterone deficiency syndrome after EBRT for localized prostate cancer are candidates for TTh. A retrospective study conducted by Davila et al assessed 6 men who received TTh after EBRT.[19] The mean Gleason score was 5. Testosterone and PSA values were measured both before and after treatment. The team found that TTh (administered by injection or transdermal gel) was effective in improving hypogonadal symptoms. 89% of the subjects elected to remain on TTh indefinitely. In addition, no significant differences were found between pre- and post-PSA levels.

Many studies published in the last 15 years demonstrate the safety of TTh in patients previously treated with localized definitive therapy for prostate cancer, and it is important to acknowledge that close follow-up may be important and is recommended by both the EAU and the AUA. Both guidelines suggest that follow-up be offered at 3, 6, and 12 months after the onset of treatment and every 6-12 months thereafter.[39,41] In addition, both organizations recommend monitoring hematocrit and performing DREs, with PSA monitoring also recommended by the EAU.[41]

## Testosterone Deficiency and Prostate Cancer Outcomes

A number of basic science studies challenge the traditional belief that androgen exposure always causes the progression and growth of prostate cancer. In 1989, Sonnenschein et al exposed LNCaP cells to different sex hormones and analyzed their response. LNCaP cells are androgen-sensitive prostate adenocarcinoma cells derived from a supraclavicular lymph node metastasis. They showed that exposure to androgens produced a biphasic response, with higher levels of exposure triggering an inhibitory effect on LNCaP cell proliferation. Their results suggested an alternative hypothesis of androgen's effect on LNCaP proliferation, with high androgen levels inducing a shutoff mechanism.[42] Umekita used LNCaP cells cultured in an androgen-depleted medium, now termed LNCaP 104-R2, and implanted them in castrated athymic mice. The tumors that formed were then exposed to testosterone propionate treatment. The testosterone propionate treatment inhibited tumor growth and significantly reduced the tumor size. Interestingly, the addition of finasteride to the tumors prevented and reversed the testosterone-induced inhibition.[43] Song and Khera studied the impacts of physiologically normal levels of androgen, by treating LNCaP cells with various levels of androgens, and studying the cell proliferation. They again found that LNCaP cells exhibit a biphasic response to testosterone. Cells with no testosterone exposure had low levels of growth, with optimized proliferation occurring at 0.23 ng/mL but increasing doses of testosterone beyond that level showed dose-dependent inhibition of growth.[44] Song and Khera then studied in vivo effects of testosterone by injecting LNCaP cells in athymic and measuring the growth of the prostate cancer tumor xenograft. They found that growth was lowest in the mice that had received an orchiectomy alone and orchiectomy plus high levels of TTh, whereas tumor incidence rate was highest in mice with no testosterone interference and orchiectomy plus low levels of testosterone. Their study again showed the biphasic response of prostate cancer to testosterone, this time in an in vivo mice model, with orchiectomy alone and orchiectomy plus high levels of TTh inhibiting proliferation of prostate cancer.[45] This increasing body of scientific evidence suggests that testosterone exposure could inhibit prostate cancer progression and potentially be protective in prostate cancer.

More recently, membrane androgen receptors (mARs) have been identified as an alternative androgen receptor, with activation leading to the regulation of responses that are distinct from the traditional intracellular androgen receptor. The binding of steroids to these non-classical membrane-bound steroid receptors leads to short-term effects, such as changes in intracellular calcium levels and cytoskeletal changes. The common effect of testosterone binding to mARs is an increase in free intracellular calcium, but the exact role that they play remains unclear. Kampa identified the distinct membrane bound testosterone receptors on LNCaP cells by using impermeable testosterone-BSA conjugate.[46] Hatzoglou showed that activation of this mAR triggers apoptosis, decreases migration and invasiveness, and dose-dependent inhibition of cell growth in prostatic cancer cells. Administration of testosterone-BSA in LNCaP cell inoculated mice also decreased the tumor mass.[47] The binding of testosterone to mARs suggests a potentially opposite effect as to the traditional AR binding. Kampa showed that activation of the mAR through exposure with testosterone-BSA simultaneously with paclitaxel augmented the antiproliferative effects of paclitaxel.[48] Discovery of this mAR and its role is significant and broadens the understanding of testosterone's antiproliferative effects on prostate cancer cells, and the potential for more therapeutic targets.

There are increasing clinical data that show that low serum testosterone may have adverse effects on the outcome of prostate cancer, whereas physiologic levels of testosterone may be protective (Table 2). Hoffman looked at 117 patients diagnosed with prostate cancer and the pathological characteristics of their prostate cancer. Compared with patients with a normal serum testosterone, they noted a correlation that patients with low serum free testosterone had higher percentage of biopsies that showed cancer (47% versus 28%, $P = .018$), and a higher incidence of a Gleason score of 8 or greater (7 of 64 versus 0 of 48, $P = .025$).[49] Morgentaler looked at hypogonadal patients and measured their serum testosterone levels and free testosterone levels and compared their rates of prostate cancer detection on biopsy. The study showed that there were higher rates of prostate cancer detection in patients with serum testosterone levels of less than 250 ng/dL, compared to patients with serum testosterone levels of more than 250 ng/dL (21% vs 12%, $P = .04$). In addition, the results also demonstrated higher rates of prostate cancer detection in patients with free testosterone levels of less than 1.0 ng/dL, compared to patients with serum testosterone levels of more than 1.0 ng/dL (20% vs 12%, $P = .04$). Increased prostate cancer detection by biopsy was associated with lower levels of testosterone.[50] Another prospective study looked at 144 patients with stage D2 prostate cancer treated with ADT and looked at what factors could influence the progression and outcome of disease. They found that initial serum testosterone greater than 10 nmol/L had a positive influence on response to treatment ($P = .0304$) and serum testosterone also had a positive impact on overall survival time (26 vs 20 months, $P = .003$). They concluded that lower testosterone levels seemed to have more aggressive disease, and worse overall survival.[51] Another study looked at hormone levels of 211 patients who underwent prostate biopsy because of abnormal PSA levels higher than 2.5 ng/ml or abnormal digital rectal examination results. Patients with free testosterone lower than 9 pg/ml had significantly higher presence of cancer than patients with free testosterone above 9 pg/ml (40.8% vs 25.6%, $P = .021$). Patients with low total testosterone below 300 nl/dL had higher cancer detection rates than patients with total testosterone above 300 (48.6% vs 29.3%, $P = .023$), again finding an association between low testosterone levels and higher

**Table 2.** Summary of studies evaluating association between level of testosterone and prostate cancer outcomes

| Author | Month Year | n | Study type | Clinical parameters | Outcomes | Conclusion |
|---|---|---|---|---|---|---|
| Hoffman et al[49] | March 2000 | 117 | Retrospective | Increased mean percent of biopsy that showed cancer | 43% of patients with low testosterone vs 22% with normal testosterone. | Patients with low free testosterone had increased mean percent of biopsies that showed cancer. |
| Morgentaler et al[50] | Dec 2006 | 345 | Prospective | Biopsy that showed cancer | 21% of patients with testosterone of less than 250 ng/dL compared vs 12% of patients with testosterone of greater than 250 ng/dL ($P = .04$). | Prostate cancer was detected at higher rates in patients with lower levels of testosterone. |
| Ribeiro et al[51] | Dec 1997 | 144 | Prospective | Response to androgen deprivation therapy and overall survival | Initial serum testosterone (>10 nmol/l) had a positive influence on response, and serum testosterone level improved overall survival. | Lower levels of testosterone were associated with more aggressive disease and a poorer overall survival. |
| Sofikerim et al[52] | 2007 | 211 | Prospective | Cancer detection on biopsy | Patients with free testosterone lower than 9 pg/ml had higher rates of cancer detection (40.8% vs 25.6), and low total testosterone had higher cancer detection rates (48.6% vs 29.3%). | Lower levels of free and total testosterone had higher rates of prostate cancer detection by biopsy. |
| Yamamoto et al[53] | Sept 2007 | 272 | Retrospective | PSA failure after RP | Patients with low (<300 ng/dl) preoperative serum testosterone levels. | Low (<300 ng/dl) preoperative serum testosterone levels were found to be an independent predictor of PSA failure. |
| Teloken et al[54] | Dec 2005 | 64 | Prospective | Positive surgical margins | Patients with serum total testosterone below 270 ng/dl had increased positive surgical margins ($P = .026$). | Patients with lower serum total testosterone had frequently more positive margins. |

rates of prostate cancer detection on biopsy.[52] This study examined preoperative serum testosterone levels and its relationship to PSA failure in patients with localized prostate cancer receiving RP as treatment alone. The results demonstrated that the 5-year PSA failure-free rate of patients with low serum testosterone was worse than patients with normal preoperative serum testosterone levels (67.8% vs 84.9%, $P = .035$), and was a significant predictor for PSA failure ($P = .021$).[53] Another study evaluated 64 patients with localized prostate cancer undergoing RP. They found that patients with serum total testosterone below 270 ng/dl had increased positive surgical margins ($P = .026$).[54] Most of these studies are limited by their retrospective nature, small study cohort, and lack of randomized control trials. A large study is needed to confirm the adverse

**Table 3.** Summary of studies assessing efficacy of bipolar androgen therapy (BAT)

| Author | Month and year | n | Study type | Clinical end point | Outcomes | Conclusion |
|---|---|---|---|---|---|---|
| Isaacs et al[57] | Oct 2012 | 4 | Prospective | Decrease in PSA | >50% decrease in PSA in the 2 patients that have completed the cycles | BAT is promising. |
| Schweizer et al[58] | Jan 2015 | 16 | Single arm case series | Decrease in PSA in at least 3 patients | >50% reduction in PSA and improved radiographic evidence | BAT is well tolerated and improved PSA. |
| Schweizer et al[59] | Sep 2016 | 33 | Single arm case series | Percent of patient had PSA <4 ng/ml after 18 months | 59% of patients has PSA<4 ng/dl at 18 months with improved QoL | BAT had preliminary efficacy and may improve QoL in patients treated with ADT. |
| Teply et al[60] | Jan 2018 | 30 | Prospective cohort | 50% decline in PSA concentration from baseline (PSA50) for BAT and enzalutamide rechallenge | 9 of 30 patients achieved a PSA50 to BAT. 29 patients completed BAT, 21 proceeded to enzalutamide rechallenge, of whom 15 (52%; 95% CI 33-71; $P < 0{\cdot}0001$) achieved a PSA50 response. | BAT is a safe therapy in castrate resistant prostate cancer and that resulted sensitization to enzalutamide. |

impact of low testosterone levels, and the potential benefit of TTh or eugonadal levels of testosterone in patients with prostate cancer.

## Testosterone Deficiency and Bipolar Androgen Therapy

ADT is the mainstay of prostate cancer, but most patients develop androgen-independent prostate cancer, which often has no effective treatment to reduce the progression of the prostate cancer. The previous studies demonstrated the possibility that low testosterone worsened prognosis of prostate cancer. Chuu derived androgen-independent (AI) prostate cells, LNCaP 104-R1 cells, by depriving androgen-sensitive prostate cells of androgens. They then studied the effects of exposing these AI cells to androgens again. The study demonstrated that exposing AI LNCaP 104-R1 cells to physiologic levels of androgens inhibited the growth of those cells. The AI LNCaP 104-R1 reverted them back to an androgen stimulated phenotype, which lead the cells to be sensitive to androgens again.[55] Another study further explored the molecular mechanism of the development of androgen independence of prostate cancer cells and found that the only change persistently found in AI prostate cancer cells was the presence of increased androgen receptor mRNA. These altered AI cells had adapted to androgen deprivation with increased androgen receptors. Exposure of these adaptive cells to a variety of androgen receptor antagonists surprisingly demonstrated an agonist response. The study concluded that androgen-specific prostate cancer cells increase androgen receptors in response to androgen deprivation, and this autoregulation is the molecular mechanism responsible for gaining androgen independence.[56] A subsequent study used this cycle of autoregulation of androgen receptors in prostate cancer cells as the molecular basis for bipolar androgen therapy (BAT) in AI prostate cancer. The study demonstrated that acute exposure of cells that have increased androgen receptor expression to high levels of testosterone resulted in increased cell death. These preclinical results provided basis to shift prostate cancer treatment away from sustained androgen deprivation toward cycling between androgen deprivation and exposure, also known as BAT. A regimen that cycled between androgen deprivation and repletion, combined with etoposide, was tested on 4 patients. It resulted in more than 50% reduction in PSA levels.[57] Although these early studies are small, they were well tolerated and demonstrated the safety of the regimen (Table 3).

A subsequent study showed that 16 asymptomatic men with low to moderate AI metastatic disease were exposed to cycles of 400 mg intramuscular and etoposide, with castrating therapy continued to suppress testosterone production, allowing for rapid reduction of testosterone to near castrate levels. BAT was well tolerated and resulted in a 50% PSA response (7 of 14) and 50% radiographic response (5 of 10). All patients eventually had PSA progressions.[58] In a subsequent study titled BATMAN, they selected patients with hormone-sensitive prostate cancer, treated them with 6 months of ADT, and patients with less than 4 ng/ml received 3 cycles of BAT. The results had 17 of 29 patients having <4 ng/ml after 18 months and improved quality of life.[59] Another recent clinical trial selected 30 asymptomatic patients that have had PSA progression on enzalutamide therapy with continued PSA rise after discontinuation of enzalutamide. Patients received PSA and reached end point if they had a 50% reduction in PSA, or they completed BAT and progressed with

enzalutamide rechallenge and then reached a 50% reduction in PSA. About 29 patients completed BAT and 21 proceeded to enzalutamide rechallenge, of whom 15 (52%; 95% CI 33-71; $P < 0{\cdot}0001$) achieved a $PSA_{50}$ response. Grade 3-4 adverse events occurred with one patient each, with hypertension, pulmonary embolism, myocardial infarction, urinary obstruction, gallstone, and sepsis, with no treatment-related deaths.[60] Although these 3 clinical trials were small, BAT therapy was well tolerated with no deaths and showed BAT as a promising potential therapy for AI prostate cancer. More large-scale clinical and randomized controlled trials need to be performed to confirm the therapeutic benefit of BAT.

### Role of TTh in Erectile Function Recovery After Prostate Cancer

To ensure effective recovery of erectile function after prostate cancer treatment, it is clear that penile tissue health at the cellular level is a critical factor to enable natural erectile function. The nitric oxide pathway is an essential signal driving the erectile function by promoting penile blood flow.[61] Marin et al demonstrated the role of testosterone in supporting the function of nitric oxide synthase; normal function was restored in castrated rats only after testosterone replacement.[62] Other studies have shown a direct correlation between testosterone and phosphodiesterase-5 (PDE-5) levels, suggesting that testosterone is involved in overall penile smooth muscle homeostasis.[63] Zhang et al demonstrated that testosterone positively regulates PDE-5 expression and in vivo responsiveness to a PDE-5 inhibitor in the rat corpora cavernosum.[63] That is, testosterone regulates nitric oxide and PDE-5 in corporal smooth muscle.

These observations were put into clinical context by Shabsigh et al, who conducted a randomized, controlled trial of testosterone, and demand-dose sildenafil versus sildenafil alone for previous PDE-5 inhibitor non-responders. The subjects were followed up with serial IIEF scores. Patients receiving testosterone supplements sustained a dramatic improvement in response to sildenafil versus the control group.[64] Admittedly, the clinical evidence supporting the role of testosterone for the erectile function is in its infancy. In fact, a dose-dependent relationship between erectile function and testosterone has been suggested, where a critical threshold has been postulated to govern adverse erectile function outcomes.[65] Regardless, the impact of testosterone on quality of life in men is well established.[66] Testosterone replacement in men treated for localized prostate cancer should be considered for 2 important reasons: (1) the scientific rationale that testosterone is a key component of erectile function and (2) the overall quality of life improvement is likely to enhance sexual interest and compliance with prostate cancer therapy. The combination of these factors justifies the role of testosterone replacement therapy in men treated for localized prostate cancer.

## DISCUSSION

Testosterone deficiency is a common condition in men that has a significant impact on overall health and quality of life. TTh is a well-established treatment option for this condition that is both effective and safe. Historically, the responsiveness of prostate cancer to androgen therapy resulted in the opinion that history of prostate cancer is a contraindication to TTh for men suffering from testosterone deficiency. As pathophysiology behind the impact of endogenous androgen therapy on prostate cancer cells has been further elucidated, evidence suggests that TTh does not endanger a patient suffering from testosterone deficiency despite a history of treated prostate cancer. The studies presented here suggest that patients treated previously with either radical prostatectomy or radiation therapy for prostate cancer do not face an elevated risk of cancer recurrence or progression as a result of TTh treatment. Evidence seems to indicate that a low-testosterone state may have deleterious effects on oncological outcomes. More recent studies as to the efficacy of BAT further supports this body of evidence. At the core of these advances is a further elucidated understanding of the effect of androgens on prostate cancer cells, as described previously.

Despite the current data illustrating the safety of TTh in men with a history of prostate cancer, resistance to TTh still persists. There is a lack of randomized placebo-controlled trials which evaluate the safety of TTh in this population. Available evidence is largely limited to case series, some with limited follow-up, inhibiting a consensus on treatment of symptomatic testosterone deficiency in patients with a history of prostate cancer. Neither the AUA nor the EAU provide strong recommendations that testosterone treatment be offered to men experiencing symptomatic testosterone deficiency. While EAU guidelines recommend that treatment be offered cautiously to those patients at low risk for recurrence, the AUA guidelines state that there is inadequate evidence to quantify the risk-benefit ratio of treatment.[15,16] The International Consultation in Sexual Medicine recommendations state that it may be reasonable to offer TTh to men with a history of prostate cancer after definitive treatment of low-risk, localized disease.[67] Expert opinion suggests that TTh treatment not be implemented until $6^3$ or 12 months[67] after radical prostatectomy with an undetectable PSA or after radiation treatment with a stable PSA. Although sufficient evidence does not exist to definitively state the safety of TTh in this population, available evidence does not point to increased risk of cancer recurrence. As such, restricting this treatment from these patients may cause undue harm by failing to address sexual health, metabolic, cardiovascular, and other manifestations of testosterone deficiency. Physicians may be reluctant to prescribe TTh for a patient previously treated for localized prostate cancer for fear of increasing risk of recurrence. Publication of large-scale studies with long-term follow-up, such as the recent Ahlering et al study may help to ameliorate the dearth of evidence necessary to determine a consensus on TTh treatment.

## CONCLUSION

Available evidence suggests that administration of TTh for the treatment of testosterone deficiency appears to be safe in patients previously treated with definitive local therapy for prostate cancer. This review validates this finding in patients treated either with surgical therapy or single or multimodal radiotherapy. Owing to the limited availability of randomized controlled trials, clinicians should remain vigilant when selecting for appropriate patients to administer TTh in secondary hypogonadal men with a history of prostate cancer.

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## STATEMENT OF AUTHORSHIP

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## REFERENCES

1. Teeling F, Raison N, Shabbir M, et al. Testosterone therapy for high-risk prostate cancer survivors: a systematic review and meta-analysis. **Urology 2019;126:16-23**.
2. Khera M, Crawford D, Morales A, et al. A new era of testosterone and prostate cancer: from physiology to clinical implications. **Eur Urol 2014;65:115-123**.
3. Kaplan AL, Hu JC, Morgentaler A, et al. Testosterone therapy in men with prostate cancer. **Eur Urol 2016;69:894-903**.
4. Huggins C, Hodges CV. The effects of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. **Cancer Res 1941;1:293-297**.
5. Debes JD, Tindall DJ. Mechanisms of androgen-refractory prostate cancer. **New Engl J Med 2004;351:1488-1490**.
6. Isbarn H, Pinthus JH, Marks LS, et al. Testosterone and prostate cancer: revisiting old paradigms. **Eur Urol 2009; 56:48-56**.
7. Morgentaler A, Traish AM. "Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth". **Eur Urol 2009; 55:310-321**.
8. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. **JAMA 2006;296:2351-2361**.
9. Morgentaler A 3rd, Conners WP. Testosterone therapy in men with prostate cancer: literature review, clinical experience, and recommendations. **Asian J Androl 2015;17:206-211**.
10. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk Stratification, Shared Decision Making, and Care options. **J Urol 2018;199:683-690**.
11. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part II: recommended approaches and details of specific Care options. **J Urol 2018;199:990-997**.
12. Khera M, Lipshultz LI. The role of testosterone replacement therapy following radical prostatectomy. **Urol Clin North Am 2007;34:549-553. vi**.
13. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. **J Urol 2004;172:920-922**.
14. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. **J Urol 2005; 173:533-536**.
15. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. **J Urol 2018;200:423-432**.
16. Salonia A, Bettocchi C, Carvalho J, et al. AU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam. Arnhem, The Netherlands: EAU Guidelines Office; 2020.
17. Nabulsi O, Tal R, Gotto G, et al. Outcomes analysis of testosterone supplementation in hypogonadal men following radical prostatectomy. **J Urol 2008;179:426-427**.
18. Davila HH, Arison CN, Hall MK, et al. Analysis of the PSA response after testosterone supplementation in patients who previously received management for their localized prostate cancer. **J Urol 2008;179:428**.
19. Khera M, Grober ED, Najari B, et al. Testosterone replacement therapy following radical prostatectomy. **J Sex Med 2009; 6:1165-1170**.
20. Sathyamoorthy K, Stein M, Mohammed O, et al. Testosterone replacement therapy in high risk patients following radical prostatectomy. **J Urol 2010;183:e577**.
21. Isbarn H, Fisch M, Huland H, et al. Testosterone treatment after radical prostatectomy for pathologically organ-confined prostate cancer; results from a multi-institutional study. **J Urol 2010;183:E576-E577**.
22. Matsushita K, Katz D, Stember D, et al. Long-term follow-up of the safety and efficacy of testosterone replacement therapy following radical prostatectomy. **J Urol 2012;187:E602-E603**.
23. Pastuszak AW, Pearlman AM, Lai WS, et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. **J Urol 2013;190:639-644**.

24. Wynia B, Lee T, Taneja S, et al. Testosterone replacement therapy in patients with prostate cancer after prostatectomy: a 5-year single center experience. **J Urol 2014;191:527.**
25. Kacker R, Hult M, Conners W, et al. Safety of testosterone therapy in men with prostate cancer. **J Urol 2014; 191:E529-E530.**
26. Ory J, Flannigan R, Lundeen C, et al. Testosterone Therapy in patients with treated and untreated prostate cancer: impact on oncologic outcomes. **J Urol 2016;196:1082-1089.**
27. Morgentaler A, Magauran D, Neel D, et al. Recurrence rates following testosterone therapy in a large clinical cohort of men with prostate cancer. **J Urol 2018;199:E206.**
28. Ahlering TE, My Huynh L, Towe M, et al. Testosterone replacement therapy reduces biochemical recurrence after radical prostatectomy. **BJU Int 2020;126:91-96.**
29. Gray H, Seltzer J, Talbert RL. Recurrence of prostate cancer in patients receiving testosterone supplementation for hypogonadism. **Am J Health Syst Pharm 2015;72:536-541.**
30. Lenfant L, Leon P, Cancel-Tassin G, et al. Testosterone replacement therapy (TRT) and prostate cancer: an updated systematic review with a focus on previous or active localized prostate cancer. **Urol Oncol 2020;38:661-670.**
31. Kardoust Parizi M, Abufaraj M, Fajkovic H, et al. Oncological safety of testosterone replacement therapy in prostate cancer survivors after definitive local therapy: a systematic literature review and meta-analysis. **Urol Oncol 2019;37:637-646.**
32. Wallis CJD, Saskin R, Choo R, et al. Surgery versus radiotherapy for Clinically-localized prostate cancer: a systematic review and meta-analysis. **Eur Urol 2016;70:21-30.**
33. Pastuszak AW, Pearlman AM, Godoy G, et al. Testosterone replacement therapy in the setting of prostate cancer treated with radiation. **Int J Impot Res 2013;25:24-28.**
34. Pastuszak AW, Khanna A, Badhiwala N, et al. Testosterone therapy after radiation therapy for low, intermediate and high risk prostate cancer. **J Urol 2015;194:1271-1276.**
35. Stish BJ, Davis BJ, Mynderse LA, et al. Brachytherapy in the management of prostate cancer. **Surg Oncol Clin N Am 2017; 26:491-513.**
36. Balbontin FG, Moreno SA, Bley E, et al. Long-acting testosterone injections for treatment of testosterone deficiency after brachytherapy for prostate cancer. **BJU Int 2014;114:125-130.**
37. Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. **Cancer 2007;109:536-541.**
38. Kadomoto S, Shigehara K, Iwamoto H, et al. Testosterone replacement therapy for patients with hypogonadism after high dose-rate brachytherapy for high-risk prostate cancer: a report of six cases and literature review. **World J Mens Health 2020;38:132-136.**
39. Tang V, Murphy DG, Moon D. Management of locally advanced (Nonmetastatic) prostate cancer. Prostate cancer (Second Edition). **Sci Clin Pract 2016:467-477.**
40. Morales A, Black AM, Emerson LE. Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. **BJU Int 2009;103:62-64.**
41. Fode M, Salonia A, Minhas S, et al. Late-onset hypogonadism and testosterone therapy — a summary of guidelines from the American Urological association and the European association of Urology. **Eur Urol Focus 2019;5:539-544.**
42. Sonnenschein C, Olea N, Pasanen ME, et al. Negative controls of cell proliferation: human prostate cancer cells and androgens. **Cancer Res 1989;49:3474-3481.**
43. Umekita Y, Hiipakka RA, Kokontis JM, et al. Human prostate tumor growth in athymic mice: inhibition by androgens and stimulation by finasteride. **Proc Natl Acad Sci U S A 1996; 93:11802-11807.**
44. Song W, Khera M. Physiological normal levels of androgen inhibit proliferation of prostate cancer cells in vitro. **Asian J Androl 2014;16:864-868.**
45. Song W, Soni V, Soni S, et al. Testosterone inhibits the growth of prostate cancer xenografts in nude mice. **BMC Cancer 2017; 17:635.**
46. Kampa M, Papakonstanti EA, Hatzoglou A, et al. The human prostate cancer cell line LNCaP bears functional membrane testosterone receptors that increase PSA secretion and modify actin cytoskeleton. **FASEB J 2002;16:1429-1431.**
47. Hatzoglou A, Kampa M, Kogia C, et al. Membrane androgen receptor activation induces apoptotic regression of human prostate cancer cells in vitro and in vivo. **J Clin Endocrinol Metab 2005;90:893-903.**
48. Kampa M, Kogia C, Theodoropoulos PA, et al. Activation of membrane androgen receptors potentiates the antiproliferative effects of paclitaxel on human prostate cancer cells. **Mol Cancer Ther 2006;5:1342-1351.**
49. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? **J Urol 2000;163:824-827.**
50. Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. **Urology 2006;68:1263-1267.**
51. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. **Am J Clin Oncol 1997;20:605-608.**
52. Sofikerim M, Eskicorapci S, Oruç O, et al. Hormonal predictors of prostate cancer. **Urol Int 2007;79:13-18.**
53. Yamamoto S, Yonese J, Kawakami S, et al. Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy. **Eur Urol 2007; 52:696-701.**
54. Teloken C, Da Ros CT, Caraver F, et al. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. **J Urol 2005;174:2178-2180.**
55. Chuu CP, Hiipakka RA, Fukuchi J, et al. Androgen causes growth suppression and reversion of androgen-independent prostate cancer xenografts to an androgen-stimulated phenotype in athymic mice. **Cancer Res 2005;65:2082-2084.**

56. Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. **Nat Med 2004;10:33-39.**
57. Isaacs JT, D'Antonio JM, Chen S, et al. Adaptive auto-regulation of androgen receptor provides a paradigm shifting rationale for bipolar androgen therapy (BAT) for castrate resistant human prostate cancer. **Prostate 2012; 72:1491-1505.**
58. Schweizer MT, Antonarakis ES, Wang H, et al. Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: results from a pilot clinical study. **Sci Transl Med 2015;7:269ra2.**
59. Schweizer MT, Wang H, Luber B, et al. Bipolar androgen therapy for men with androgen ablation Naïve prostate cancer: results from the phase II BATMAN study. **Prostate 2016; 76:1218-1226.**
60. Teply BA, Wang H, Luber B, et al. Bipolar androgen therapy in men with metastatic castration-resistant prostate cancer after progression on enzalutamide: an open-label, phase 2, multicohort study. **Lancet Oncol 2018;19:76-86.**
61. Burnett AL. Novel nitric oxide signaling mechanisms regulate the erectile response. **Int J Impot Res 2004;16-(Suppl 1):S15-S19.**
62. Marin R, Escrig A, Abreu P, et al. Androgen-dependent nitric oxide release in rat penis correlates with levels of constitutive nitric oxide synthase isoenzymes. **Biol Reprod 1999;61:1012-1016.**
63. Zhang XH, Morelli A, Luconi M, et al. Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum. **Eur Urol 2005;47:409-416.**
64. Shabsigh R, Kaufman JM, Steidle C, et al. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. **J Urol 2004;172:658-663.**
65. Armagan A, Kim NN, Goldstein I, et al. Dose-response relationship between testosterone and erectile function: evidence for the existence of a critical threshold. **J Androl 2006;27:517-526.**
66. Maggi M, Schulman C, Quinton R, et al. The burden of testosterone deficiency syndrome in adult men: economic and quality-of-life impact. **J Sex Med 2007;4:1056-1069.**
67. Morgentaler A, Traish A, Hackett G, et al. Diagnosis and treatment of testosterone deficiency: updated recommendations from the Lisbon 2018 International Consultation for sexual medicine. **Sex Med Rev 2019;7:636-649.**