

# Testosterone therapy and prostate cancer

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**Abstract:** The use of exogenous testosterone to treat hypogonadism in the men with a history of prostate cancer (CaP) remains controversial due to fears of cancer recurrence or progression. Due to the detrimental impact of hypogonadism on patient quality of life, recent work has examined the safety of testosterone therapy (TTh) in men with a history of CaP. In this review, we evaluate the literature with regards to the safety of TTh in men with a history of CaP. TTh results in improvements in quality of life with little evidence of biochemical recurrence or progression in men with a history of CaP, or *de novo* cancer in unaffected men. An insufficient amount of evidence is currently available to truly demonstrate the safe use of TTh in men with low risk CaP. In men with high-risk cancer, more limited data suggest that TTh may be safe, but these findings remain inconclusive. Despite the historic avoidance of TTh in men with a history of CaP, the existing body of evidence largely supports the safe and effective use of testosterone in these men, although additional study is needed before unequivocal safety can be demonstrated.

**Keywords:** Hypogonadism; testosterone; hormone replacement; prostate cancer (CaP); prostatectomy; radiation therapy

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## Introduction

Male hypogonadism is defined as the presence of both low serum testosterone levels as well as symptoms that can include decreased libido, erectile dysfunction, loss of vitality, loss of lean muscle and bone density, fatigue, anemia and depression (1). The prevalence of hypogonadism has proven difficult to accurately determine, with the highest reported prevalence reported in 2006 when Mulligan *et al.* found that 40% of men over age 45 had symptomatic hypogonadism (2). Alternatively, the European Male Aging Study (EMAS) reported a prevalence of only 2.1%, and the Boston Area Community Health Study (BACHS) estimated the prevalence of hypogonadism to be 5.6% among men 30–79 years old (3,4). Importantly, these studies incorporated both the presence of low testosterone levels as well as symptoms as part of the

definition of hypogonadism. Prostate cancer (CaP) is also most common among older men and accounts for one of every five cancer diagnoses in men (5). Mortality from CaP has dropped by over 50% in the past two decades, with an increase in survivorship that is significantly higher than the overall increase in cancer survivorship. This improved survivorship in men with CaP is primarily attributed to earlier cancer detection and treatment, and is leading to growing population of CaP survivors; it is estimated that 20% of all cancer survivors are CaP survivors (6).

Over the past decade, the use of testosterone therapy (TTh) has dramatically increased. Between 2001–2011 the number of testosterone prescriptions tripled, with increases among all age groups. Baillargeon and colleagues found that 3.75% of the U.S. male population over 65 years old had been prescribed some form of TTh (7). This increase in

prescribing practices is in part due to the known benefits of therapy, which can decrease mortality, improve lipid parameters, decrease body fat, and improved sexual function (8-10). The negative physiological sequelae of hypogonadism are also well established, and include bone reabsorption, which can lead to osteoporosis and osteopenia; TTh can normalize bone density (11-13). Multiple studies have also shown that testosterone has important immunomodulatory effects, including regulation of neutrophils and monocytes (14-17). Along with the benefits of TTh, several potential risks have been identified. Among these, the most discussed are the potential adverse cardiovascular (CV) effects of TTh and the impact of testosterone on CaP. Numerous studies have reported a relationship between TTh and CV risk, with studies observing an increased risk of CV events in men with both low and high testosterone levels. Most recently, a handful of studies have observed a positive correlation between testosterone levels and CV events, especially in older men, and have ultimately led to changes in testosterone labeling (18-21). More recently, Baillargeon and colleagues found that the risk of CV events was the same in both hypogonadal men treated and not treated with TTh. Upon further examination, however, a modest decrease in CV risk was observed in the testosterone treated cohort (22,23).

For decades, the use of TTh in men with a history of CaP has been controversial. The seminal 1941 study by Drs. Charles Huggins and Clarence Hodges found that castration resulted in regression of metastatic CaP, implicating androgens in the CaP growth (24). Subsequent work supported a role for testosterone in recurrence or progression of existing CaP, especially in the setting of advanced CaP (25,26). As such, an androgen dependent model of CaP remains the main objection to TTh in men with a history of CaP (27). However, clinical studies have failed to show a persuasive link between CaP and TTh that would limit the treatment of hypogonadal men with a history of CaP. With an aging population, increasing CaP survivorship and the quality of life that can be restored with TTh, TTh is worth considering in CaP survivors. In this review, we examine the literature with regards to the risk of CaP as a function of serum testosterone levels, as well as what is known regarding the safety of TTh in men with a history of CaP.

## Methods

A literature search was conducted using PubMed to identify relevant, current studies as well as historical perspectives

on the data and attitudes examining TTh in the setting of CaP. Search terms used included: “prostate cancer”, “hypogonadism”, “testosterone replacement therapy”, “TTh”, “active surveillance (AS)”, “radical prostatectomy”, and “radiation therapy”.

### *CaP and low serum testosterone*

The link between low endogenous testosterone levels and CaP has been extensively studied. Men with low endogenous testosterone levels have increased rates and severity of CaP at diagnosis, including extraprostatic invasion (28). The first study to recognize this was published in 1996 by Morgentaler *et al.*, in which the authors identified CaP in 14% of 77 men with low serum testosterone levels, a normal digital rectal examination (DRE) and a PSA <4.0 ng/mL. Though the small sample size limited the generalizability of these initial results, the relationship between endogenous testosterone levels has been examined repeatedly over the past two decades (*Table 1*) (29). In 2006, Morgentaler *et al.* examined 345 hypogonadal men with a PSA <4.0 ng/mL, and found CaP in 21% of men with a testosterone level of  $\leq 250$  ng/dL. In contrast, only 12% of men with a testosterone level  $>250$  ng/dL were found to have CaP ( $P=0.04$ ) (33). A 2013 prospective study of 206 men with benign prostatic hyperplasia (BPH) or CaP found that low serum testosterone levels (less than 240 ng/dL) were an independent predictor of CaP risk [ $P=0.004$  with an OR for CaP of 0.7 (95% CI: 0.55–0.89)] (30). In 2010, Shin *et al.* studied 568 men undergoing prostate biopsy and divided them into low ( $<385$  ng/dL) and high ( $>385$  ng/dL) testosterone groups. Using multivariate regression analysis to compare these groups, the authors found a significantly higher incidence of CaP in the low testosterone group (38.9% *vs.* 29.5%,  $P=0.018$ ). In addition to low serum testosterone levels, the study identified increasing age, high PSA, and low prostate volume as factors associated with increased CaP risk (31).

Low serum testosterone has also been linked to more aggressive, higher-grade CaP. In 2000, Hoffman and colleagues retrospectively analyzed 117 men with CaP. Men with low serum testosterone levels ( $<300$  ng/dL) were found to have a higher number of positive cores on biopsy (43% *vs.* 22%,  $P=0.013$ ) and were more likely to have Gleason sum 8 or greater disease (7 of 64 *vs.* 0 of 48,  $P=0.025$ ) when compared with men with normal testosterone levels (34). A similar retrospective analysis of 137 men with CaP showed that high serum testosterone is correlated with lower stage

**Table 1** Studies examining the relationship between low endogenous testosterone levels and prostate cancer

References	Number of pts	Study type	Endogenous TTh level	CaP outcomes
Morgentaler <i>et al.</i> (29)	77	Retrospective	T <300 ng/dL or free T <1.6 ng/dL	CaP incidence of 14% (11/77)
Mearini <i>et al.</i> (30)	206	Prospective	≤2.4 ng/mL	14.2% of patients had clinically locally advanced or metastatic CaP, and 57.1% have a pathological locally advanced CaP
			≤0.5 ng/mL	40% of patients have clinically locally advanced or metastatic CaP, and 60% has a pathological locally advanced CaP
Shin <i>et al.</i> (31)	568	Prospective	<3.85 ng/mL	CaP incidence 38.0% (vs. 29.5% high testosterone group)
Karamanolakis <i>et al.</i> (32)	718	Prospective	<3.0 ng/mL	CaP incidence 30% (29/97)
Morgentaler <i>et al.</i> (33)	345	Retrospective	<250 ng/dL	CaP incidence 21% (vs. 12% in men with T >250 ng/dL)
Hoffman <i>et al.</i> (34)	117	Retrospective	T <300 ng/dL or free T <1.5 ng/dL	CaP incidence 43% (vs. 22%)
García-Cruz <i>et al.</i> (35)	137	Prospective	<346 ng/dL	Tumor burden 53% (vs. 32% in men with T >346 ng/dL); tumor bilaterality 50% (vs. 25.5% in men with T >346 ng/dL)
Isom-Batz <i>et al.</i> (36)	326	Retrospective	<385 ng/dL	Associated with advanced pathological stage (OR 2.3, 95% CI: 1.1–5.0; P=0.03)
Lane <i>et al.</i> (37)	455	Prospective	<220 ng/dL	Higher frequency of Gleason 4–5 disease (OR 2.4, 95% CI: 1.01–5.7; P=0.48)
Botto <i>et al.</i> (38)	431	Prospective	<3 ng/mL	Higher frequency of Gleason 4 disease (47% vs. 28%)
Salonia <i>et al.</i> (39)	673	Prospective	Total T <1 ng/mL	Higher incidence of seminal vesicle invasion (OR 3.11; P=0.006)
Teloken <i>et al.</i> (40)	64	Retrospective	<2.7 ng/mL	Increased positive surgical margins (P=0.026)

pts, patients; CaP, prostate cancer; TTh, testosterone therapy; T, testosterone; OR, odds ratio.

disease based on DRE (P=0.02) and PSA (P=0.05). Lower serum testosterone was also correlated with higher rates of bilateral disease (P<0.01) (35). Yet another similarly designed study examined the pretreatment hormonal status of 326 men who underwent radical prostatectomy and examined biochemical recurrence (PSA >0.4 ng/mL with a documented increase after treatment). While the study found no relationship between PSA and testosterone levels (P=0.4), low testosterone was found to inversely correlate with pathological stage, clinical stage and biopsy grade (P=0.01) (36).

Recent prospective studies have also shown that low pretreatment testosterone level is a predictor of higher Gleason score. A 2008 study examining 455 men found that

low serum testosterone was not predictive of biochemical recurrence, tumor volume or disease progression, but that it was associated with Gleason 4–5 disease [odds ratio (OR) 2.4, 95% CI: 1.0–5.7; P=0.048] (37). While the literature mainly supports hypogonadism as a risk factor for CaP and increased severity of disease, controversy still remains in the absence of large prospective, controlled studies. A retrospective analysis of 673 men with CaP showed hypogonadism to only be predictive of seminal vesicle invasion and did not show a relationship between pretreatment hypogonadism and a higher incidence of CaP (39). Lastly, beyond incidence and severity, low pretreatment testosterone has been linked to an increased likelihood of positive surgical margins after radical prostatectomy (P=0.026) (40).

**Table 2** Studies examining the relationship between normal and high serum testosterone levels and prostate cancer

References	Number of pts	Study type	Endogenous TTh level	CaP outcomes
Shaneyfelt <i>et al.</i> (41)	2,310	Cohort/nested case-control	–	Highest quartile 2.34 times more likely to develop CaP than those in lowest quartile (95% CI: 1.30–4.20)
Gann <i>et al.</i> (42)	612	Retrospective	Highest vs. lowest quartiles	OR 2.60, 95% CI: 1.34–5.0; P=0.004
Yano <i>et al.</i> (43)	420	Retrospective	4.2±2.6 ng/mL	Pretreatment T higher in pts diagnosed with CaP than in pts diagnosed with BPH (3.6±1.4 ng/mL); P=0.007
Salonia <i>et al.</i> (44)	724	Cohort	Lowest and highest circulating T	Both associated with high-risk CaP (nonlinear U-shaped behavior)
Porcaro <i>et al.</i> (45)	220	Retrospective	TT >15.5 nmol/L	Higher risk for tumors Gleason sum ≥8 (OR 1.31 vs. TT <15.5 nmol/L)
Salonia <i>et al.</i> (46)	605	Prospective	Continuous variable	Early BCR in 5.6% (PSA ≥0.1 ng/mL) within 24 months after RP
Roddam <i>et al.</i> (47)	3,886	Prospective, pooled 18-study analysis	Quartiles	Not significant
Muller <i>et al.</i> (48)	3,255	REDUCE trial	<2.88 ng/mL	Not significant
Platz <i>et al.</i> (49)	460	Prospective, nested case-control	Highest vs. lowest quartiles	Not significant
Mearini <i>et al.</i> (50)	65	Prospective	>2.4 ng/mL	OR 0.15, 95% CI: 0.03–0.68; P=0.014
Ahmadi <i>et al.</i> (51)	194/317	Prospective, matched controls	High TT, FT controls	(P<0.001); protective against CaP, enhanced by each decade of increasing age
Røder <i>et al.</i> (52)	227	Prospective	>11 ng/mL	Reduced risk of biochemical failure (HR 0.53, 95% CI: 0.31–0.90; P=0.02)
Imamoto <i>et al.</i> (53)	222	Retrospective	>4.9 ng/mL	Positive prognostic value
Yamamoto <i>et al.</i> (54)	272	Retrospective	>300 ng/dL	84.9% five-year PSA failure-free survival rate (vs. 67.8% pts with serum T <300 ng/dL)

pts, patients; CaP, prostate cancer; TTh, testosterone therapy; OR, odds ratio; T, testosterone; TT, total testosterone; FT, free testosterone; BCR, biochemical recurrence; PSA, prostate specific antigen.

### CaP and normal or high serum testosterone levels

Studies examining the relationship between normal and high pretreatment serum testosterone levels and CaP have yielded often conflicting results (*Table 2*). A number of studies have reported an increased risk of CaP with high pretreatment serum testosterone levels. In 1996, Gann *et al.* reported a positive association between men in the highest quartile of testosterone levels and an increased risk of CaP (42). Similarly, a meta-analysis published in 2000 found that when stratified by pretreatment testosterone levels, men in the highest quartile were 2.34 times more likely to develop CaP (95% CI: 1.30–4.20). While this meta-analysis adjusted for BMI, age and serum hormone levels, it only

incorporated data from two studies (41). A 2007 study enrolling 420 men found that while there was no significant relationship between pretreatment testosterone levels and prostate biopsy results, men with PSA <10 ng/mL eventually diagnosed with CaP (mean T 420±260 ng/dL) had higher serum testosterone levels than men diagnosed with benign prostatic disease (mean T 360±140 ng/dL) (P=0.007) (43).

The relationship between Gleason score and high serum testosterone levels has also been examined. In 2014, Porcaro *et al.* found a relationship between men with higher normal pretreatment testosterone levels (T >447 ng/dL) and Gleason sum ≥8 disease (P=0.0004) when compared to men with lower testosterone (45). In 2016, Porcaro *et al.* found

that high testosterone levels predicted an increased risk of Gleason score upgrading (OR, 1.06;  $P=0.027$ ) (55).

In contrast to the above findings, several studies have found no relationship, or even a protective relationship, between high testosterone levels and CaP risk. The Endogenous Hormones and CaP Collaborative Group used conditional logistic regression to assess 18 prospective studies that included 3,886 men with incident CaP and 6,438 controls. No associations between the risk of CaP and serum testosterone concentrations were identified (47). The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial and Platz *et al.* (retrospective review of 460 men) both reported a lack of association between normal or high testosterone and CaP incidence (48,49). A handful of studies have observed a decreased risk of CaP in the setting of high testosterone levels. In 2004, Stattin *et al.* conducted a case-control study of 708 men with CaP and found a modest but significant decrease in CaP risk among men with higher pretreatment testosterone levels ( $P=0.05$ ) (56). Two similarly designed studies also reported that men with higher testosterone levels had a lower risk of CaP (50,51). A lower risk of biochemical recurrence and better prognosis for both localized and metastatic CaP after radical prostatectomy have also been observed in men with higher pretreatment testosterone levels (52-54).

#### ***Prostate specific antigen (PSA) and testosterone levels***

The secretion of PSA and growth of CaP are under androgenic control. As such, androgen deprivation remains a major component of advanced CaP treatment (57). However, changes in PSA *in vivo* do not linearly correlate with serum testosterone levels. A 1998 study found no significant change in PSA levels in 31 healthy volunteers 21-39 years old after administration of either 100,250 or 500 mg testosterone for 15 weeks at any dose, supporting an androgen receptor (AR) saturation point, above which no further increases in PSA or CaP growth are observed (58). In healthy men, the AR saturation point is thought to be at a serum testosterone concentration of 150-200 ng/dL (59). Among men with castrate serum testosterone levels, a rise in testosterone levels correlates with a rise in PSA, but only until the androgen receptor is saturated (60). Studies aimed at correlating androgen levels and PSA have had limited success. Mearini *et al.* set out to determine whether serum testosterone levels could augment the use of PSA levels in distinguishing CaP from BPH in men in whom CaP was suspected due to their elevated PSA. Testosterone level was

identified as an independent predictor of CaP risk, as both a continuous and binary variable with sensitivity and specificity varying as a function of testosterone thresholds established in the analysis. For testosterone levels below 240 ng/dL, sensitivity and specificity of predicting CaP were 32% and 91.3%, respectively. For testosterone levels below 50 ng/dL, sensitivity and specificity were 9.4% and 99%, respectively (30).

#### ***Models to explain clinical findings***

As a result of the findings of Huggins and Hodges in 1941, treatment of hypogonadal men with a history of CaP has remained controversial. However, since the early 1990's, both *in vitro* and *in vivo* studies have largely argued against prior work supporting CaP growth in the setting of rising testosterone levels. Work over the past two decades has yielded conflicting results and has shown that the relationships between androgen levels, healthy prostate tissue and CaP is more complex than originally thought. Two recent models that have been proposed to explain the more recent clinical findings are the prostate saturation and time-dependence models.

The prostate saturation model was first alluded to in 1981 by Fowler and Whitmore, who concluded that normal serum testosterone levels may not be correlated with maximal CaP growth and that growth only varied with androgens at sub-physiologic levels (26). Morgentaler and Traish sought to reconcile why low testosterone levels resulted in regression of CaP but high levels could not consistently be linked to CaP growth or spread. They postulated that because tumor growth varied with testosterone levels only in the setting of castrate testosterone levels, and not in eugonadal men, that this may be related to the saturation point of the AR, and that any stimulation of prostate tissue would cease when the AR saturation point had been reached (61). These authors published a literature review in 2009 that supported their model and suggested the AR saturation point was below the generally accepted 300 ng/dL threshold for clinical hypogonadism (62). Overall, however, there are a few studies that support the prostate saturation model (58). In 2014, Morgentaler *et al.* published a double-blind placebo-controlled study of 274 hypogonadal men. One of the relevant factors predicting an increase in PSA during testosterone gel treatment was a baseline testosterone level of  $<250$  ng/dL. No significant variation in PSA levels in men with baseline testosterone  $>250$  ng/dL was observed (63). A similar study enrolling 451 men found comparable results and concluded

that physicians should exercise caution when treating hypogonadal men with very low testosterone levels (64). There is also support for this prostate saturation model *in vitro* using the androgen-responsive CaP tumor cell line, LNCaP. Bologna *et al.* found that the growth rate of these cells was only enhanced at the lowest T concentrations (0.001  $\mu$ M) and that there was a modest but statistically insignificant protective effect at higher concentrations (65). Using the same cell line, Arnold *et al.* found that cell proliferation increased at low T concentrations but that at higher concentrations even logarithmic increases in T could not enhance growth (66).

The time-dependence model was initially presented in 2012 by Salonia *et al.* This model was developed based on the observation that an increased risk of CaP was observed both at near-castrate as well as high serum testosterone levels. The authors concluded that the relationship between CaP and androgen levels followed a non-linear u-shaped distribution. Salonia *et al.* dubbed this the time dependence theory because they postulated that the healthy endocrine tissue relied on temporal stimulation of different androgen levels and that these fluctuations were absent in men who went on to develop CaP (28,44). Broad support for the time-dependence theory does not currently exist, in large part because the relationship between high endogenous testosterone levels and CaP remains unclear.

Both the prostate saturation and time-dependence models account for the observation that CaP growth in culture is androgen-dependent at low levels. This is clinically relevant because these levels (0.23 ng/mL and between 1 and 2 ng/mL for the cell lines LNCaP and MDA PCa 2b, respectively) are at the low end of physiologic testosterone levels (67). This is thought to explain CaP recurrence after androgen deprivation therapy (ADT) as the androgen levels normalize from castrate levels after treatment (68). In men with androgen-sensitive cancers, keeping androgen levels low is the standard of care despite the tradeoff of hypogonadal symptoms (69). Most men who undergo ADT will eventually develop castration-resistant prostate cancer (CRPC). Many cellular mechanisms have been attributed to this phenomenon including: increased expression of both wild type and ligand-independent AR variants, AR gene amplification, and AR mutations (70-74).

While cells can adapt to androgen deprivation well, even CRPC cells are inhibited by supraphysiologic androgen levels (75,76). Hatzoglou *et al.* found dose-dependent inhibition of cell growth could be induced using testosterone, leading to increased apoptosis and decreased prostate cell

migration, adhesion, and invasiveness in human LNCaP cells (77). Mechanistically, supraphysiologic androgen levels facilitate nuclear stabilization of ligand-bound AR, which leads to apoptosis by inhibiting DNA relicensing (78,79). High androgen levels can also cause lethal double stranded DNA breaks, which can be pharmacologically exploited using single-agent oral etoposide, an inhibitor of topoisomerase II $\beta$  and DNA repair (80). This *in vitro* finding led to a 2015 pilot study using bipolar androgen therapy (BAT) to treat metastatic CaP. Fourteen patients with metastatic CRPC were given testosterone cypionate (400 mg intramuscular) and etoposide (100 mg oral daily) to rapidly bring them from castrate to supraphysiologic testosterone levels; this cycle was repeated three times. After BAT, the patient's testosterone levels were brought back to castrate levels. Astonishingly, 7 of 14 patients had PSA decline in response to AR-directed therapy (such as abiraterone, enzalutamide, or bicalutamide) given after BAT, suggesting that BAT could re-sensitize patients to therapy (81). Additional *in vitro* evidence supports the efficacy of BAT therapy. Song and Khera demonstrated a dose-dependent inhibition of CaP cell proliferation as physiologic androgen levels increased from the normal range, starting at 4 ng/mL testosterone (67). While many studies have examined the relationship between testosterone and CaP, there are many ongoing limitations including: intra-individual variation in testosterone measurements, and clinical applicability of findings across age, race, BMI and CaP status.

### *TTh across CaP treatment modalities*

#### **Radical prostatectomy**

Radical prostatectomy remains the preferred treatment modality in CaP patients under 70 years old with an aging population and increase in CaP survivorship, TTh after radical prostatectomy is an important area of investigation (82). Recent studies support the conclusion that TTh in men with a history of CaP is effective in treating hypogonadism without having a significant impact on CaP recurrence or progression.

A 2004 study by Kaufman and Graydon followed seven hypogonadal men started on TTh with a history of CaP treated with radical prostatectomy. After following the patients for 1–12 years, no CaP recurrence was observed, though the small sample size was a significant limitation of the work (83). In 2005, Agarwal and Oefelein followed ten men post radical prostatectomy recently started on TTh and found significant improvements in quality of

life attributed to decreases in hot flashes and increases in energy without CaP recurrence or detectable increase in PSA after 19 months (84). In 2009 a retrospective review of 57 hypogonadal men ages 53–83 years old with CaP treated with radical prostatectomy who were started on TTh and followed for a mean of 36 months found no increase in PSA or biochemical recurrence despite an increase in mean testosterone levels from 255 to 459 ng/dL ( $P < 0.001$ ) (85). More recently, Pastuszak *et al.* reviewed 103 hypogonadal men post radical prostatectomy treated with TTh and 49 non-hypogonadal men treated only with radical prostatectomy. Of the 103 hypogonadal men, 77 had non-high risk and 26 had high risk CaP. A clinically insignificant, but statistically significant increase in PSA levels was observed in the treatment group among both high and non-high risk patients; a similar PSA increase was not observed in the reference group. However, among men with high risk CaP, four in the treatment group, in contrast with eight in the reference group, had a biochemical recurrence. The study concluded that although PSA levels could rise during TTh, this was not correlated with an increased incidence of CaP recurrence and that TTh could be appropriate in the treatment of hypogonadal men, even in the setting of high risk CaP (86).

### Radiation therapy

The relationship between TTh in the setting of men with CaP treated using radiation therapy has also been studied. One study followed five men started on TTh after external beam radiation therapy (EBRT) observed small increases in PSA with no CaP recurrence, and emphasized the benefits of TTh including a reduction in hot flashes, increased energy and improved erectile function (87). A similar retrospective chart review that followed 31 hypogonadal men treated with TTh with a history of CaP treated with brachytherapy for 1.5–9 years observed an increase in PSA of  $< 0.5$  ng/mL in 30 patients (96.7%) and  $< 1$  ng/mL in all patients with no CaP recurrences observed (88). A subsequent retrospective review of 13 hypogonadal men with CaP treated with brachytherapy or external beam radiation therapy on TTh found no significant increases in PSA or CaP recurrence. However, after a mean of 29.7 months follow-up, significant increases in testosterone levels were observed, along with improvements in hypogonadal symptoms (89). Interestingly, a 2014 study by Balbontin *et al.* following 20 men on TTh after brachytherapy reported a decrease in PSA from a baseline of 0.7 to 0.1 ng/dL after treatment ( $P < 0.001$ ). The authors also evaluated sexual

function using the Sexual Health Inventory for Men (SHIM) questionnaire and observed a significant increase in scores from 16.1 at baseline to 22.1 in men on TTh ( $P = 0.002$ ) (90). A 2015 retrospective study by Pastuszak *et al.* examined CaP outcomes by risk group in 98 hypogonadal men after radiation therapy treated with TTh. A low rate of biochemical recurrence (6.1% of the cohort) and a clinically insignificant rise in mean PSA were observed [ $0.08$  ng/mL at baseline to  $0.09$  ng/mL ( $P = 0.05$ )] (91).

Though incompletely studied, in light of the above data, TTh should be considered in men after radiation therapy for CaP in conjunction with close surveillance. However, further study using randomized, controlled studies is needed.

### *Patients on AS, at risk for developing CaP, or who have high risk CaP*

The American Cancer Society predicts 180,890 new cases of CaP in 2016, with 35–40% of those being low-risk (92). AS avoids overly aggressive treatment of low-risk CaP by periodically assessing the risk of CaP progression (93). Given the recent observations that do not demonstrate an increased risk of CaP incidence or progression in the setting of normal serum testosterone levels, TTh in the setting of CaP under AS, or in men at risk for developing CaP, may be reasonable. In 2003, Rhoden *et al.* studied 75 hypogonadal men who had been on TTh for at least a year. After prostate biopsy due to abnormal DRE or elevated PSA, 55 men had no evidence of prostatic intraepithelial neoplasia (PIN) and 20 had evidence of PIN with no overt cancer present. Men in both groups had similar PSA levels before TTh treatment. Small increases in PSA levels were also seen in men with and without PIN ( $0.33 \pm 0.6$  and  $0.25 \pm 0.6$  ng/dL, respectively,  $P > 0.05$ ) with only one man with PIN eventually developing CaP (94). In 2016, Kacker *et al.* found that when compared to 96 hypogonadal men on AS alone, the 28 hypogonadal men on AS and concurrent TTh had comparable CaP progression on biopsy over 3 years (95). Also in 2016, Ory *et al.* examined 82 hypogonadal men with CaP treated using either radiation therapy, radical prostatectomy, AS, cryotherapy or high-intensity focused ultrasound and on TTh. Of the eight men on AS, none required treatment of CaP after a mean follow-up of 27 months (96). Preliminary data examining men with advanced CaP on TTh also support efficacy of TTh without an increased risk of CaP progression. Ferreira *et al.* followed five hypogonadal patients with a history of advanced CaP on

TTh. After 18 months, only one patient experienced a PSA increase and none of the men had CaP metastasis (97).

Few studies to date have studied TTh in men with active CaP and have reported predominantly positive outcomes in men with CaP, with a common theme of caution. A 2016 review concluded that although the data on using TTh in men on AS are limited, preliminary studies show no, or minimal, increased risk compared to the quality of life improvements seen with treatment of hypogonadism (98). Conversely, a 2011 study following 25 men with CaP reported highly variable outcomes after starting TTh. The authors urged caution in treating these patients and concluded that an international registry to collect more data would be the only way to address whether TTh was safe in men with CaP (98,99). While the preliminary studies of TTh in the setting of AS appear to demonstrate the relatively safety of treating hypogonadism with TTh in this setting, it is important to note that none of these studies were randomized or controlled and that more work must be done before unequivocally determining the safety of such treatment.

## Conclusions

The use of TTh in the setting of CaP remains controversial due to a lack of definitive, appropriately powered prospective controlled studies. However, available evidence supports the overall conclusion that TTh in patients with a history of both treated or untreated CaP is both safe and effective, particularly in men with low risk malignancies. TTh in men with a history of high-risk CaP is supported by small, retrospective studies that overall show no increased risk of CaP recurrence or progression in these men. In light of the available evidence, we recommend careful consideration of TTh in all men with an history of CaP while weighing the potential risks with the improvement in quality of life so clearly evidenced with TTh. Treatment of hypogonadism, especially in men with low risk CaP with significant impact on quality of life as a result of hypogonadism, is warranted. Men with high-risk CaP pose a more difficult scenario, but with appropriate surveillance, the available evidence supports the safe use of TTh in these men as well.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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