Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

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To cite this article: Abraham Morgentaler & Monica Caliber (2019): Safety of testosterone therapy in men with prostate cancer, Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2019.1666103

To link to this article: https://doi.org/10.1080/14740338.2019.1666103

Accepted author version posted online: 07 Sep 2019.

Safety of testosterone therapy in men with prostate cancer

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Abstract

Introduction: The use of testosterone therapy (TTh) in men with prostate cancer (PCa) is relatively new, and controversial, due to the longstanding maxim that TTh is contraindicated in men with PCa. Scientific advances have prompted a reevaluation of the potential role for TTh in men with PCa, particularly as TTh has been shown to provide important symptomatic and general health benefits to men with testosterone deficiency (TD), including many men with PCa who may expect to live 30-50 years after diagnosis.

Areas covered: This review outlines the historical underpinnings of the historical belief that TTh "fuels" PCa and the experimental and clinical studies that have radically altered this view, including description of the saturation model. The authors review studies of TTh in men with PCa following radical prostatectomy and radiation therapy, in men on active surveillance, and in men with advanced or metastatic PCa.

Expert opinion: TTh provides important symptomatic and overall health benefits for men with PCa who have TD. Although more safety studies are needed, TTh is a reasonable therapeutic option for men with low-risk PCa after surgery or radiation. Data in men on active surveillance are limited, but initial reports are reassuring.

Key words: active surveillance, androgens, androgen deprivation therapy, prostate cancer, prostate cancer radiation, prostatectomy, saturation model, PSA, testosterone deficiency, testosterone therapy

Article highlights

- Many men with a history of prostate cancer suffer from testosterone deficiency.
- Testosterone therapy in these men improves symptoms and confers significant health benefits, including improved sexual function, increased energy and sense of wellbeing, loss of fat mass and gain in lean mass, resolution of anemia, and increased bone mineral density.
- Although no large, long-term, controlled studies have yet been performed to provide definitive evidence regarding the safety of testosterone therapy in men with prostate cancer, the available data is reassuring.
- Testosterone therapy may be reasonably offered to symptomatic men with testosterone deficiency who have low-risk disease after treatment for localized prostate cancer with surgery or radiation.
- Testosterone therapy in men on active surveillance is less well established, however, several initial reports have shown progression rates comparable to those seen in men who did not receive testosterone therapy.
- New clinical trial data suggests there may even be a therapeutic role for testosterone therapy in men with advanced prostate cancer.

1. Introduction

Prostate cancer (PCa) is the second most frequent cancer in men [1]. PCa incidence is increasing while PCa mortality is decreasing in most countries worldwide [2-4]. In 2018 there were 164,690 new cases of PCa and 29,430 deaths in the US.[5] PCa survival has improved over the past decades; in Western countries the 5-year survival rate for localized disease is nearly 100%, with a 10-year survival rate of 95% [6]. The substantial longevity of PCa survivors raises important medical and ethical questions about the use of testosterone therapy (TTh) in these men, which has historically been considered contraindicated in men with PCa, or even the suspicion of PCa, due to the belief that androgens promote PCa growth and aggressiveness. For this reason, there had been scant clinical experience with TTh in men with PCa until approximately twenty years ago, even though testosterone has been available as a therapeutic agent since the mid-1930s.

Testosterone deficiency (TD) causes a wide range of bothersome symptoms, and contributes to a number of general health issues. The consequences of TD are the same whether or not a man has a history of PCa. Symptoms include sexual dysfunction, depressed mood, cognitive decline, hot flashes, fatigue, loss of muscle mass and strength, and irritability [7]. TD also reduces bone mineral density, increases the risk for development of obesity [8], type 2 diabetes [9] and cardiovascular events [10], and is associated with increased all-cause and CVD mortality [11-13]. TTh in men with TD ameliorates or reverses these symptoms, and specifically has been shown to improve sexual function, mood, muscle mass, insulin sensitivity, components of the metabolic syndrome, decrease fat mass, increase bone mineral density, and resolve anemia [15].

A few contradictory studies raised concern that testosterone therapy may be associated with increased risk of myocardial infarction (MI), ischemic stroke or mortality [14,15]. However, these studies had a number of serious methodological limitations which question the validity of the data [16-19], and culminated in a petition for retraction.[20]

An overwhelmingly large number of studies show that TTh is associated with a reduced risk of myocardial infarction, stroke, cardiovascular and all-cause mortality [21-36]. Thus, the 70-year-old prohibition against TTh in men with PCa poses a challenging clinical dilemma, since there are large number of men diagnosed or treated for PCa who

may live 30-50 more years, and many of these men may suffer from symptomatic TD. It is a matter of considerable practical concern whether these men may safely receive TTh [37].

The fear of stimulating PCa has been the most important reason physicians give for their reluctance to offer TTh to men [38]. This fear is supported by labels for testosterone (T) products which provide warnings that TTh should be avoided in men with PCa, and even in men with a suspicion of PCa. Over the last 20 years there has been a re-evaluation of the prohibition against TTh in men with PCa, and a modest published experience of TTh in these men. Physician attitudes appear to be changing in some countries but not others [39,40]. Before discussing the safety of TTh in men with PCa, we will review the historical underpinnings of the widespread belief that T fuels PCa, and outline how modern data has refuted the overly simplistic idea that T is “bad” for the prostate.

2. Testosterone and prostate cancer: an historical perspective on a modern myth

Historically, prostate cancer – both active and treated - has been an absolute contraindication to TTh. The belief that testosterone has detrimental effects on the prostate, the so called "androgen hypothesis" arose from two small studies in the 1940s in which men with metastatic PCa demonstrated clinical and biochemical improvement with androgen deprivation via castration or estrogen treatment, and conversely rapid PCa progression with testosterone administration [41,42]. Rather than concluding that exogenous testosterone attenuates the effects of surgical castration, the authors concluded that prostate cancer is activated by testosterone [43].

It has to be pointed out that these historical studies that gave rise to the androgen hypothesis only provided evidence for the role of testosterone in the progression/regression of prostate cancer, not the development (initiation) of prostate cancer de novo. Whether testosterone plays any role – good or bad - in the actual development of prostate cancer, as opposed to its further growth, was not addressed. Furthermore, these observations were made in a special population (castrated men) and may not have relevance to TTh in men with milder forms of TD [44], such as that

commonly seen in primary care. Nevertheless, the myth was born that testosterone is uniformly “bad” for the prostate under all circumstances.

Medical students and doctors have since been taught that high testosterone levels promote the development of prostate cancer, that low testosterone is protective, and that the administration of testosterone to a man with existing prostate cancer is like "pouring gasoline on a fire"[45]. Fear of prostate cancer remains a major concern and is one of the main reasons for doctors' reluctance to prescribe TTh even for T-deficient men without PCa [38,46-48], depriving many symptomatic men of helpful treatment. Although the dramatic effects of (ADT) in PCa are indisputable [49], a large body of current evidence fails to support the concept that increasingly high levels of testosterone or DHT lead to ever-greater growth of benign or malignant prostate tissue (see below). It is critical to note that the androgen hypothesis was accepted prior to the discovery of the androgen receptor and PSA (prostate specific antigen), and before the availability of reliable serum testosterone assays. It should therefore not be surprising that some predictions of the androgen hypothesis would turn out to be false when submitted to rigorous scientific investigation.

3. Paradigm shift - the saturation model

By the 1980s it was axiomatic that high T levels contributed to the development of PCa and its aggressive nature, and that low levels of T were protective [50]. These two “arms” of the androgen hypothesis prevented any use of TTh except in the most severe cases of T deficiency in young men, such as the presence of pituitary tumors, or following pituitary resection, or anorchia, as it was clear that these young men required testosterone for male development and function. The first direct evidence that the androgen hypothesis was flawed was the observation that men with symptomatic low T levels, normal PSA and normal DRE had a surprisingly high rate (14%) of PCa on sextant biopsy [51]. Since then, a growing number of studies have demonstrated that *low* levels of total [52,53], free [53-55] or bioavailable [55] serum testosterone at PCa diagnosis are associated with more aggressive PCa, biochemical recurrence, and predict poor PCa survival. A meta-analysis of endogenous T levels and PCa prognosis found that in patients with advanced PCa higher testosterone levels before ADT were

associated with a 42% reduced risk of death (HR = 0.58; 95% CI, 0.45-0.74; P < .0001) [56].

In direct contradiction to predictions based on the androgen hypothesis, it has now been conclusively demonstrated that PCa risk is unrelated to the entire range of naturally occurring testosterone levels in the populations studied [57]. Numerous studies show no correlation between endogenous testosterone levels, PSA, prostate volume or PCa [57-60]. The Endogenous Hormones and Prostate Cancer Collaborative Group conducted a comprehensive analysis of pooled worldwide epidemiologic data from 18 prospective studies, comprising a study population of 3886 men with PCa and 6438 age-matched controls, found no relationship between PCa risk and serum concentrations of testosterone, calculated free testosterone or DHT [57]. In a large observational study of 10,311 men who were treated with TTh and 28,029 men who did not receive TTh, after a follow-up of up to 7.5 years, men who received TTh had a lower risk of being diagnosed with PCa than men who did not receive TTh [61]. Furthermore, the longer these men were on TTh, the lower the PCa risk [61].

The paradoxical findings that androgen deprivation appears to have therapeutic benefits for men with advanced PCa, yet higher endogenous T or TTh appear unrelated to increased PCa risk or aggressiveness, have been reconciled by the saturation model, which was first described by Dr. Morgentaler in 2006 [62]. The saturation model explains the paradoxical observations that prostate tissue is sensitive to changes in testosterone levels at low concentrations, but becomes insensitive to changes in testosterone levels at higher concentrations [50,62]. This response is consistent with the observation that testosterone exerts its prostatic effects primarily via binding to the AR, and that maximal testosterone-AR binding is achieved at testosterone levels below the physiologic range [50,62]. Consistent with the saturation model, two studies that investigated prostatic effects of supraphysiological dosing of testosterone for 15 weeks [63] and 5 months [64], revealed no change in PSA or prostate volume.

Changes in testosterone levels below the point of maximal testosterone-AR binding can elicit substantial changes in prostate cancer growth, as seen with castration, or with testosterone administration to castrated or severely hypogonadal men. In contrast, once maximal testosterone-AR binding is reached, further increasing testosterone levels

results in little, if any, further prostate stimulation. Hence, there is a threshold where increasing testosterone levels reach a limit - the saturation point - beyond which there is no further androgen-driven prostate tissue growth (figure 1). PSA will reliably increase (within the normal rage) to a modest degree with TTh if baseline T is below the saturation point - approximately 250 ng/dL (although the exact T level that defines the saturation point varies among men) - but not if baseline T is above the saturation point [65-67].

Maximal testosterone-AR binding (i.e., saturation) occurs at fairly low androgen concentrations. The androgen receptor in human prostate tissue becomes saturated at approximately 4 nmol/L (120 ng/dL) in vitro, corresponding to approximately 8-8.3 nmol/L (240-250 ng/dL) in vivo (due to the presence of binding hormones) [68,69].

The saturation model also applies to androgen sensitive PCa cells; PCa cell growth is accelerated rapidly with testosterone exposure up to the saturation point, but thereafter the dose-response curve stabilizes and increasing testosterone will no longer provide further PCa growth [45,62]. Indeed, several studies have confirmed that high-normal to supraphysiological concentrations of androgens will actually suppress PCa growth in vitro and in vivo [70-72].

4. TTh and PCa risk in men with no PCa history

The Androgen receptor (AR) is present in many tissues, including normal and malignant prostate tissue, and mediates the effect of androgens. Free testosterone enters the cell, is reduced by 5-alpha reductase to dihydrotestosterone (DHT), which has a higher affinity for the AR compared with testosterone. The weaker androgenic potency of testosterone compared to that of dihydrotestosterone resides in its weaker interaction with the androgen receptor [73]. The complex of androgen-AR then transposes to the cell nucleus where it binds to androgen response elements on DNA and stimulates production of androgen-dependent gene products. Interestingly, finasteride blocks reduction of testosterone to DHT, causing reduction in prostate volume. In the large Prostate Cancer Prevention Trial, finasteride reduced the number of diagnosed PCa compared to placebo, but did not alter the number of high grade PCa cases [74].

The saturation model explains the results found in numerous studies of TTh and PCa risk in men with no PCa history. In a randomized, double blind, placebo-controlled trial, testosterone therapy showed no effect on prostate tissue histology, tissue biomarkers, gene expression, cancer incidence, or severity [75]. Interestingly, in this study intraprostatic concentrations of T and DHT did not increase during 6 months of T administration despite substantial increases in serum concentrations, suggesting a homeostatic hormonal mechanism within the prostate. Notably, the UK Androgen Study found that the incidence of PCa during long-term TTh for up to 20 years is equivalent to that expected in the general population [76]. Testosterone treatment had no statistically significant effect on total PSA, free PSA or free/total PSA ratio, and any initial PSA change had no predictive relationship to subsequent diagnosis of PCa [76]. Wallis et al. even found that men who received TTh had a lower risk of becoming diagnosed with PCa, and that the longer these men were on TTh the lower the PCa risk, compared to men not receiving TTh [61].

In healthy men, administration of supra-physiologic doses of testosterone (weekly injections of 500-600 mg of testosterone enanthate to healthy volunteers for up to 16 weeks) resulted in no significant increase in PSA nor prostate volume [63,77,78]. In hypogonadal men treated with testosterone, levels of PSA typically rise up to PSA levels seen in eugonadal men, but stay within the normal range [65]. This elevation in PSA and prostate volume commonly occurs during the initial 3-6 months after initiation of TTh, and then stabilize with continued TTh [79-82].

The Registry of Hypogonadism in Men (RHYME) is a large, multi-national prospective registry of men with testosterone deficiency, which was designed and powered specifically to assess prostate cancer outcomes in men receiving testosterone therapy compared to untreated men with testosterone deficiency or general population estimates [83]. The primary aim was to examine prospectively the association between testosterone therapy and prostate health outcomes, including prostate cancer incidence and BPH progression in hypogonadal men naive to testosterone therapy, who are diagnosed and treated according to current standard-of-care guidelines. Of 999 men with diagnosed testosterone deficiency, 750 (75%) were started on testosterone therapy. Follow-up assessments were performed at 3, 6, 12, 24, and 36 months. It was

found that the proportion of positive biopsies was nearly identical in men on testosterone therapy (37.5%) compared to non-treated men (37.0%). There were no differences in PSA levels, total IPSS, or the IPSS obstructive sub-scale score. Lower IPSS irritative sub-scale scores were reported in testosterone treated men compared to untreated men. It was concluded that testosterone therapy does not increase prostate cancer incidence or BPH/LUTS progression compared to matched untreated men [83]. Prostate cancer incidence rates in RHYME were similar to rates reported in large population studies and with findings from other single country registries. PSA levels were minimally affected and slight improvements in voiding symptoms were seen in men on testosterone therapy [83].

In line with these findings, two meta-analyses of intervention studies, which focused on analyzing potential adverse effects of TTh, did not find any significant differences in prostate outcomes between TTh vs. placebo treated men [78,84]. Specifically, the most recent meta-analysis published in 2010 demonstrated no difference in the rates of prostate cancer, need for prostate biopsy, international prostate symptom score (IPSS), increase in PSA, or total number of prostate-related adverse events when comparing the testosterone groups with the placebo groups [78].

Hence, compelling evidence shows that men with higher testosterone levels within the physiological range – whether endogenous or achieved with TTh – appear to be at no greater risk for PCa than men with lower serum testosterone, or those who did not receive TTh.

5. Testosterone and PCa cells – in vitro data

PCa cells in vitro and in animal studies grow more optimally in the presence of androgens than without androgens, and also demonstrate a dose-response curve at lower concentrations [71]. However, this response changes once physiologic and supraphysiologic concentrations are achieved [71]. Thus, the relationship between T and PCa is not a straight-line curve, as once believed, where higher androgen concentrations result in proportionally greater PCa growth.

A possible therapeutic role for supraphysiological T concentrations in men with advanced PCa, i.e. that T can have inhibitory effects on malignant prostate cells, is

supported by a number of in vitro and xenograft studies with PCa cell lines [70,85-87]. Whereas androgen-dependent cell lines such as LnCaP show a dose-response curve with increased cell growth associated with increased in vitro androgen concentrations [71], further increases in androgen concentrations results in suppression of growth, beginning at the upper end of normal concentrations and into the supraphysiological range.[71] Chuu et al. demonstrated not only growth suppression with high androgen concentrations, but also restoration of androgen dependent phenotype in PCa cultures that had developed androgen-resistance [70].

Interestingly, testosterone triggers inhibition of PCa cell proliferation [85,88], growth suppression [70] and apoptotic regression of human PCa cells in vitro and in vivo [86]. It is particularly notable that testosterone can suppresses the proliferation of castration-resistant PCa cells [87,89] (see below). Mouse xenograft studies using androgen-sensitive prostate cancer cells, including LnCaP, ARCaP, and PC-3 with over-expressed androgen receptor, showed that high-dose androgens cause growth inhibition and G1 cell cycle arrest by regulating c-Myc, Skp2, and p27Kip via the androgen receptor [90]. Although the concept will strike many as new that supraphysiological androgen concentrations may have an inhibitory effect, it was shown 30 years ago that LnCaP cells have a biphasic response to increasing DHT concentrations, with initial increase in growth, followed by growth inhibition at higher concentrations [85].

6. TTh in men with TD and PCa

The growing body of evidence exposing the flaws of the androgen hypothesis and dogmatic belief that T is “bad” for the prostate under all circumstances and at all T concentrations, coupled with a growing

understanding of the significant widespread negative health effects of TD cumulated in a paradigm shift

away from testosterone as a prostate cancer inducer [50]. This shift opened the door for clinicians to start to examine the effects of TTh in men with a history of PCa, as well as in men with existing low-grade PCa on active surveillance. Not surprisingly, these studies have shown that TTh results in significant reductions in bothersome symptoms

and improved quality of life and wellbeing in PCa patients [91-97]. A recent meta-analysis confirmed the safety of TTh in prostate cancer survivors after definitive local therapy [98]. Interestingly, the overall biochemical recurrence rates in patients who received TTh after definitive treatment was lower than reported rates in the literature after primary definitive treatment alone [99]. Table 1 summarizes safety outcomes of these studies, which are briefly described below. In table 2 we summarize recommendations for the use of TTh in men with PCa.

6.1 TTh after radical prostatectomy

The first study examining TTh in the context of PCa was published in 2004 by Kaufman and Graydon [100]. Seven men, six with Gleason 6 and one with Gleason 7, who had been treated with RP received TTh for 2-13 years, which increased mean T levels from 97 to 434 ng/dL. Although follow-up times were varied and the sample size was small, no biochemical or clinical evidence of CaP recurrence was seen in any patient [100].

In 2005 Agarwal and Oefelein reported no biochemical recurrences with TTh for 1-11 years after RP in 10 men with higher risk disease, including 7 with Gleason 7 disease and 1 with Gleason 8 pathology and 2 with Gleason 6 [91].

In 2009 Khera et al. [102] published a study of a larger group of 57 patients, including men with Gleason

6 (n = 24), Gleason 7 (n = 26), and Gleason 8 (n = 4), who were treated with TTh after RP. T levels increased from 255 to 459 ng/dL. No biochemical recurrences were observed after a follow‐up of 13 months (range: 1–99).

The study by Leibowitz et al. 2010 [103] is notable in that it achieved very high serum T levels during TTh. It included 96 patients, 25% of whom had been treated with RP. Despite high-dose TTh, in 40% of patients TTh was not associated with increasing PSA levels, even over a long period. However, 60% of men had increasing PSA levels that triggered discontinuation of TRT. It is reassuring that for most of the patients, biochemical progression was not associated with clinical or symptomatic PCa progression. Further, symptomatic PCa progression was absent despite the inclusion of men with high-risk high-grade disease, and even patients with metastatic disease. In most cases, discontinuing TTh resulted in rapid and dramatic declines in PSA levels, such that most men did not need immediate anti-neoplastic therapy. Men who started

TTh with lower PSA values had a decreased risk of PSA progression. This study is a good example of the saturation model by showing that high-dose TTh and achievement of supra-physiological serum levels of testosterone did not correlate with PCa progression.

Pastuszak et al. 2013 [104] examined 103 patients receiving TTh following RP. This series is notable for inclusion of 26 patients at high risk for biochemical recurrence, based on Gleason 8–10, positive surgical margins, or positive lymph nodes. The study had a comparison group of 49 post-RP patients, including 15 high‐risk cases, who did not receive TTh. T levels increased from 261 to 460 ng/dL and mean follow‐up was 27 months. Biochemical recurrence was 4% in the T‐treated group and 16% in the untreated comparison group.

6.2 TTh after radiation therapy

In 2006 Sarosdy et al. [101] reported the results of TTh in 31 men who had undergone brachytherapy, of whom 11 were treated with a combination of brachytherapy and external beam radiation and 14 also underwent adjuvant androgen deprivation therapy (ADT). Patients had Gleason 5 (n=6) Gleason 6 (n = 19), Gleason 7 (n=6), and Gleason 8/9 (n=3). Mean duration of TTh was 4.5 years, with a mean follow‐up of 5 years (range: 1.5–9 years). None of the men developed biochemical recurrence, and all had PSA levels < 1 ng/mL at last follow‐up, including 74% with PSA < 0.1 ng/mL.

Morales et al. [92] examined 5 patients who received TTh following external beam radiation treatment. TTh raised T levels from 150 to 507 ng/dL and follow‐up ranged from 6 to 27 months. None of the men had a PCa recurrence as determined by DRE and PSA testing at regular intervals.

Pastuszak et al. [93] reported on a group of 13 men who received TTh following radiation treatments, including 3 men treated with brachytherapy, 10 treated with external beam radiation, and four with combined radiation treatment. Patients had Gleason 6 (n=4), Gleason 7 (n=7), and Gleason 8 (n=4). TTh was initiated at a mean of 13.5 months following completion of radiation, though in some cases as soon as 2.6 months. Mean follow‐up was 29.7 months (range: 2.3–67). None of the men developed PCa recurrence. Mean PSA at last follow‐up was 0.66 ng/mL (range: 0.16–1.35 ng/mL).

In 2014 Balbontin et al. [96] reported on 20 men treated with injectable T undecanoate for a mean of 14 months (range: 3–36) following brachytherapy. Patients had Gleason 6 pathology or lower (n=16),
Gleason 3 + 4 (n=3), and Gleason 8 (n=1). The patient with Gleason 8 also underwent external beam radiation. Median follow‐up was 31 months (range: 12–48). PSA declined from the start of TTh to last follow‐up from 0.7 to 0.1 ng/mL. None of the men developed a PSA recurrence.

6.3 TTh in men on active surveillance

Active surveillance (AS) is a disease-management strategy of close monitoring of men with low-risk prostate cancer. The goal of active surveillance is to defer PCa treatment unless there is evidence for subsequent development of higher risk disease, or a patient chooses curative treatment [111]. Men on AS undergo regular examinations with PSA and follow‐up prostate biopsies, with definitive treatment reserved for men with evidence for disease progression or more aggressive tumor grade [112]. Among men on AS, approximately one‐third experience PCa progression [113].

In 2009 Morgentaler published the first report of TTh in a patient with untreated low‐risk PCa on AS; an 84‐year‐old man who was seen for symptoms of TD [114]. His total T level was 400 ng/dL, but free T was reduced. PSA was 8.1 ng/mL and prostate biopsy revealed Gleason 6 cancer in both lobes. He refused treatment for PCa, but requested TTh, which was initiated after informed consent regarding possible cancer progression. Serum T increased to 699 ng/dL and free T to 17.1 pg/mL. PSA declined to a nadir of 5.2 ng/mL at 10 months, increased slightly to 6.2 ng/mL at 21 months, and then declined to 3.8 ng/mL at 24 months after addition of dutasteride for voiding symptoms. No clinical PCa progression was noted [114]. This case was the first support for the notion that PCa growth may not be adversely affected by changes in serum T above the castrate range.

A subsequent study by Morgentaler et al. published in 2011 examined 13 symptomatic men with TD on AS [97]. Mean age was 58.8 years and Gleason score at initial biopsy was six in 12 men and seven in 1 man. TTh was provided for up to 8 years. Serum T levels increased from 238 to 664 ng/dL. PSA levels declined from 5.5 to 3.6 ng/mL, although the change did not meet conventional levels of

statistical significance. Prostate volume was unchanged. None of the men demonstrated definite cancer progression or metastases. Two men had apparent PCa upgrading that was not confirmed with further examination [97]. The same year a cautionary note was raised by Morales, who reported variable PSA responses in 7 men during TTh while on AS [115].

In 2016 Kacker et al. [94] published a study of 28 men with TD who received TTh while on AS for Gleason 3 + 3 and Gleason 3 + 4 PCa. Baseline PSA was 3.29 ng/mL. A comparison group of 96 men on AS was identified at the same institution who also had low serum T concentrations but did not receive TTh. TTh increased serum T levels from 328 to 469 ng/dL and mean follow‐up was 39 months. Progression was defined as an increase in grade, number of positive cores, or percentage of core involvement with cancer. Results showed a trend towards a lower rate of overall biopsy progression (increase in either Gleason score or PCa volume) in men receiving TTh (32.1% vs 44.7%) [94]. Similar rates of upgrading of Gleason score were noted for each group, with 3 of 28 cases (10.7%) in the TTh group and in 9 of 96 (9.4%) in the untreated group. These progression rates are similar to other published AS studies involving men who did not receive TTh and where testosterone status was unknown [101-102].

Hashimoto et al. [108] investigated multiparametric prostate magnetic resonance imaging (mpMRI) findings in 12 patients before and after TTh for 1 to 10 years, while on active surveillance for low-risk prostate cancer. TTh significantly increased T levels from 203 ng/dL to 517 ng/dL, PSA (3.3 ng/mL to 4.2 ng/mL), and prostate volume (39.4 cm^3 to 55.2cm^3). Prostate Imaging Reporting and Data System Version 2 (PI-RADSv2) scores were unchanged in 10 patients, in whom no biopsy progression was seen. In the remaining 2 patients PI-RADSv2 scores increased and both showed Gleason score upgrade on follow-up biopsy.

San Francisco et al. [116] analyzed factors that predict PCa progression during AS. Using multivariable regression analysis, it was found that low free testosterone levels were associated with a several-fold increased risk of disease upstaging and progression to definitive treatment. For total testosterone, a threshold value of 346 ng/dL had significant discriminant power, with shorter times to definitive treatment for men with total testosterone levels below 346 ng/dL [116].

Ory et al. [109] reported progression results in men with PCa treated with various modalities, including 8 men on AS, who received TTh for 33 months. Their testosterone level increased from 5.2 to 15.2 nmol/L, and PSA rose from 3.9 to 5.2 ng/mL. None of these men demonstrated progression.

7. Use of testosterone therapy as treatment for PCa

Recently, the observation that supraphysiological androgen concentrations suppress PCa growth and promote a less aggressive phenotype has been incorporated into protocols for the treatment of advanced PCa. In 2015 Shweizer et al. [117] reported results of a protocol called bipolar androgen therapy (BAT) in which men with castrate resistance PCa on leuprolide underwent treatment with 400mg intramuscular injection of testosterone cypionate, every 4 weeks. This resulted in supraphysiological T concentrations for approximately two weeks or longer, followed by return to castrate levels once the T injection wore off. This cycling of high and low T concentrations resulted in reduced PSA in seven of 14 men, and demonstrable radiographic responses in 5 of 10 evaluable patients [117].

Additional promising results using BAT have been reported in other populations. The BATMAN trial evaluated the safety and efficacy of BAT in patients with asymptomatic hormone sensitive PCa with low metastatic burden or non-metastatic biochemically recurrent disease [118]. Testosterone cypionate or enanthate was administered intramuscularly (IM) at the dose of 400 mg every 28 days (day 1, 29, and 57), a dose/schedule shown to generate a rapid rise in serum testosterone levels to the supraphysiologic range (>1500 ng/dL) 2 days post-injection, with a decline to near castrate level (100 ng/dL) 28 days post-injection. ADT was continued throughout the study to allow rapid cycling from near castrate to supraphysiologic range T following T injections. Results showed the primary endpoint was met, with 17/29 men (59%, 90% confidence interval: 42-74%) having PSA <4 ng/mL at 18 months. QoL improved following the first cycle of BAT, as measured by the SF-36, FACT-P, and IIEF surveys.[118]

The first prospective trial to investigate BAT in patients with metastatic castration-resistant prostate cancer after progression on enzalutamide showed that BAT is safe

and tolerable [119]. Notably, BAT resulted in favorable responses, and also re-sensitized to enzalutamide in most patients undergoing re-challenge [119]. BAT is a promising new application of testosterone therapy in advanced and metastatic PCa, and possibly also in patients with asymptomatic hormone sensitive PCa with low metastatic burden or non-metastatic biochemically recurrent disease.

8. The frontier of clinical practice

We now routinely offer TTh to men with PCa who have undergone treatment with surgery or radiation, or who are on active surveillance. Men are advised that there has been a longstanding belief that TTh is contraindicated in men with PCa, but that this view is undergoing reevaluation based on published clinical experiences and more sophisticated understanding of the relationship of T and PCa. Men are further advised that there are yet no large, controlled studies demonstrating safety, and that there is therefore an unknown degree of risk that TTh may cause PCa progression, morbidity, or mortality. An informed consent is signed.

Our experience with 190 men with PCa treated with TTh for a mean follow-up of nearly 4 years was presented at the 2018 annual meeting of the American Urological Association, including 86 men following radical prostatectomy, 49 men following radiation therapy, and 47 men on active surveillance. Mean age was 68, with a range of 41 to 88 years. Rates of progression or recurrence compared favorably to published series for similar groups of men who never received TTh.

Based on the foregoing science and clinical experience, we have now also treated approximately 12 selected individuals with either biochemical recurrence or metastatic disease. Three of these men have received TTh for 3 years or more. Several of these men had already experienced the benefits of TTh prior to diagnosis of PCa, and desired the improved quality of life they achieved with TTh. Others are symptomatic from TD, and still others wish to avoid the standard approach of lowering serum T with ADT. Men with metastatic disease undergo a modified version of BAT, termed mBAT, in which there is continuous use of high-dose T cypionate injections every 2 weeks for a total of 8 weeks, followed by 4 weeks of ADT or an androgen blocker such as enzalutamide. Quality of life has been improved greatly in all men. While PSA rises in all individuals

during the periods of TTh, there has been no cases of precipitous disease progression based on clinical or radiographic parameters, or death. These data are being tabulated for publication.

9. Conclusion

The longstanding belief that raising serum T will necessarily cause PCa to grow or become more aggressive is contradicted by multiple lines of evidence. Today, it is understood that there is a finite, limited ability of androgens to stimulate PCa growth, based on the saturation model. Specifically, PCa growth is exquisitely sensitive to changes in androgens at low concentrations, and is indifferent to concentration changes through the physiological testosterone range. At supraphysiological concentrations, in vitro and in vivo results demonstrate suppression of PCa growth.

In light of this continuing reevaluation of the biological relationship between T and PCa, numerous case series have reported reassuring results with TTh in various populations of men with PCa. The symptomatic and general health benefits of TTh in these men may outweigh the theoretical but as yet unproven risk of PCa progression or recurrence. New clinical trial data suggests there may even be a role for TTh as *treatment* for men with advanced PCa.

These results represent nothing less than a complete conceptual revolution over the last twenty years regarding what was once an axiomatic principle in oncology. While TTh cannot yet be considered completely “safe” for men with PCa, the health implications of continued investigation in this area are immense, and it will be exciting to see what the next twenty years of research will show.

10. Expert opinion

We have entered a new era of testosterone and prostate cancer. Over the last two decades there has been a revolution in our understanding of the relationship of androgens and PCa, resulting in numerous published series of TTh in men with PCa. The reassuring results of those trials provide a basis for offering TTh to selected men with PCa, particularly those who appear cured of PCa after definitive therapy. However, it must be acknowledged that we still lack large-scale controlled studies performed over

many years in order to clearly determine safety of TTh in men with a history of PCa. Furthermore, there is a medico-legal consideration, in that product labels for all testosterone products warn against the use of TTh in men with PCa.

Nonetheless, the high prevalence of PCa and the extended lifespan of men successfully treated for PCa mandates that we take an objective look at the evidence regarding the use of TTh in men with a history of PCa. Testosterone deficiency not only causes bothersome symptoms, including loss of sexuality and impaired sense of wellbeing, but is also associated with important general health consequences, including obesity, cardiovascular disease, type 2 diabetes, osteoporosis and mortality. If TTh truly increased morbidity and mortality from PCa, then it would be reasonable to avoid such treatment. However, it is now apparent that the original prohibition against TTh in these men arose from an overly simplistic notion that any increase in T would promote PCa growth and aggressiveness. That belief is not supported by the evidence, and numerous studies now report reassuring results with TTh in men with PCa.

In the absence of definitive safety studies, one must be cautious regarding TTh in men with PCa. The safest populations for TTh are those whose cancer was low-risk and appears cured following radical prostatectomy or radiation therapy, especially if PSA remains undetectable or appropriately low for several years after treatment. Somewhat more risk is entailed for high-risk disease and with short follow-up after definitive treatment, since recurrent disease is more likely in these populations. Of course, these men are at increased risk for recurrence even without TTh, so TTh cannot definitely be identified as the cause if recurrence occurs. The amount of published data in men on active surveillance is scant. Since approximately one in three men on AS who do not receive TTh will progress, clinicians and patients must be prepared for this eventuality, and must understand that if a man is also receiving TTh when this occurs, it is impossible to know based on current evidence whether TTh contributed to progression.

The successful treatment of men with advanced PCa with BAT contradicts the decades-long belief that raising T in these men is uniformly dangerous. Part of this argument in the past has been that testosterone flare with LHRH agonists is associated with rapid and serious adverse events, including death. Two reviews of the flare data have shown this argument to be without merit [120,121]. Yet standard therapy for men with

advanced PCa remains ADT. The use of TTh in these men, including with BAT or mBAT, must be considered investigational only.

One of the principles of evidence-based medicine is that concepts that fail to withstand scientific scrutiny are to be discarded. Such a time has come for the belief that T causes enhanced growth of PCa and that TTh is an absolute contraindication in men with PCa.

Funding

This paper was not funded.

Declaration of interests

A Morgentaler is a consultant for Aytu and Antares, a meeting participant for Acerus, and has received a research grant from Endo. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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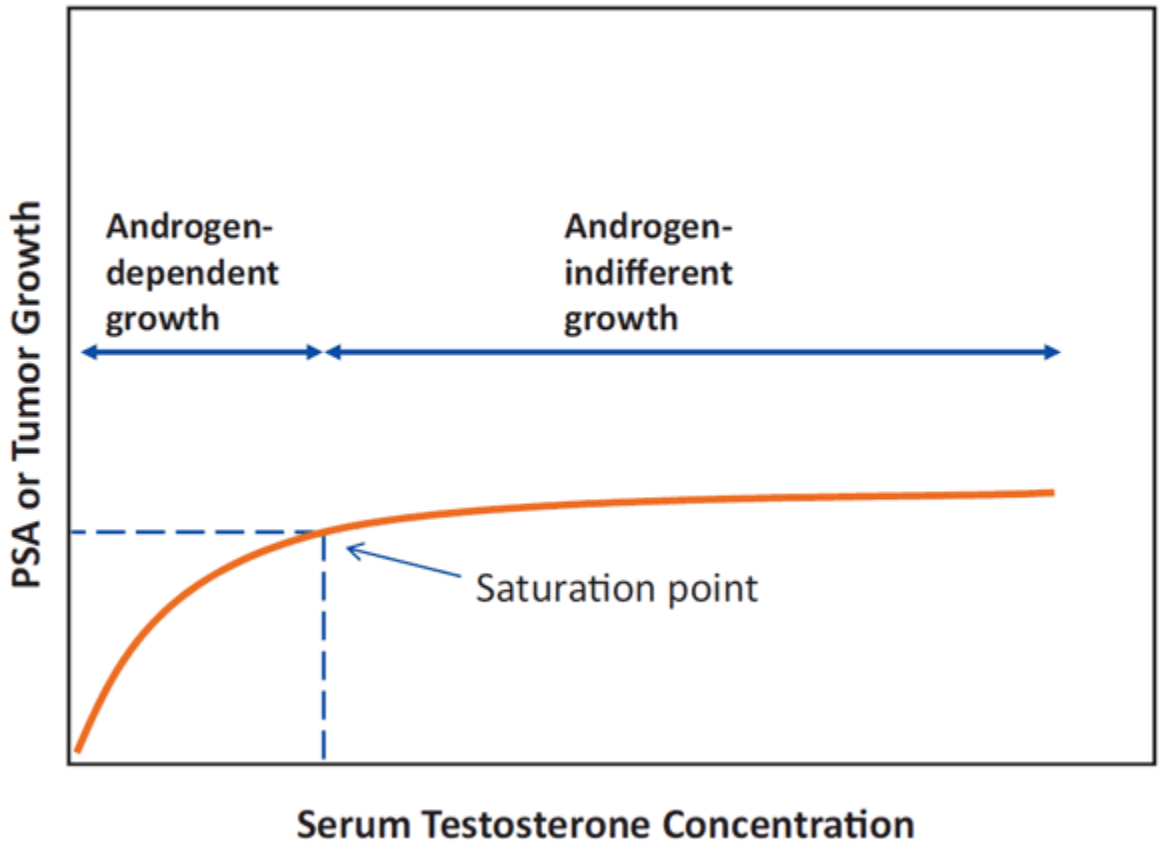
Figure 1:

The saturation model. Increasing T levels result in PSA elevation and/or prostate tissue growth until the saturation point is reached, beyond which T does not further stimulate the prostate.



From Khera et al. 2014 [45]

Table 1: Studies investigating the safety of TTh in men with active or treated PCa.

Study	No. of patients	Treatment	Follow-up months *	Gleason score (number of patients)	PSA pre-/post TTh (ng/mL)	T levels pre-/post TTh (ng/dL)	Comment
Kaufman and Graydon 2004 [100]	7	RP	24	6 (6) 7 (1)	<0.1 / <0.1	97 / 434	No biochemical or clinical evidence of PCa recurrence.
Agarwal and Oefelein 2005 [91]	10	RP	19	6 (2) 7 (7) 8 (1)	<0.1 / <0.1	197 / 591	No biochemical recurrence.
Sarosdy et al. 2007 [101]	31	BT EBRT ADT	60	5 (3) 6 (19) 7 (6) 8/9 (3)	na / <1	188 / 489	Transient increases in PSA in 1 patient. No patients stopped TRT because of cancer recurrence or documented cancer progression.
Khera et al. 2009 [102]	57	RP	13	6 (24) 7 (26) 8 (4)	0.005 / 0.005	255 / 459	No patient had biochemical recurrence.
Morales et al. 2009 [92]	5	EBRT	14.5	6 (2) 7 (1) 8 (2)	0.1–0.97 / <0.1–1.08	150 / 507	None of the men had a recurrence of prostate cancer, as determined by DRE and PSA testing at regular intervals.
Leibowitz et al. 2010 [103]	96	RP EBRT BT ADT	15 (1-83)	≤3 + 3 (33) 3 + 4, 4 + 3 (17) (22)	variable	na / 1391 (range 303–2637)	41 men (43%) had PSA progression while on TTh. 7 of these men were found to have

				4 + 4, 3 + 5 (12) (1) 4 + 5, 5 + 4 (5) (3) 5 + 5 (10) (2) missing (1)			concurrent radiological progression. 31 men continued on TTh to the end of the study period, with a median (range) duration of 36.7 (2–79) months.
Morgentaler et al. 2011 [97]	13	AS	30	6 (12) 7 (1)	5.5 / 3.6	238 / 664	Follow-up biopsies in all men; no definite PCa progression in any patient. No increase in mean PSA or prostate volume. No cancer in 54% of follow-up biopsies.
Pastuszak et al. 2013 [93]	13	BT EBRT	29.7	6 (4) 7 (7) 8 (2)	0.30 / 0.66	178 / 368	No patient had biochemical recurrence.
Pastuszak et al. 2013 [104]	103	RP	27.5	<6 (1) 6,7 (72) ≥8 (9)	0.004 / 0.007	261 / 460	Included 26 men with high-risk PCa and positive margins or nodes or Gleason score >8. Comparison group of 49 men with RP without TTh. 4 PSA recurrences in TTh group (4%), 8 PSA recurrences in

							comparison group (16%).
Balbontin et al. 2014 [96]	20	BT	31	≤6 (16) 7 (3) 8 (1)	0.7 / 0.1	343 / 587	No cases of rising serum PSA, prostate cancer progression or recurrence.
Bryant et al. 2014 [95]	23	PT	38			238 / 497	No biochemical recurrence. At last follow-up, PSA was ≤0.5 for 14 of 23 (61%) patients, <1 for 19 of 23 (83%) patients, and <3 for all of the patients.
Kaplan et al. 2014, 2015 [105,106]	1,181	RP EBRT Brachytherapy AS/WW	72	Well ** (9752) Moderate (87 786) Poor (50 635)	n/a	n/a	TTh was not associated with increased overall or cancer-specific mortality. In time-varying analysis, longer duration TTh was not associated with increased mortality or greater need for ADT.
Pastuszak et al. 2015 [107]	98	BT EBRT	40.8	≤6 (47) 7 (28) 8 (7) 9 (4)	0.08 / 0.09	209 / 420	Among patients at high risk. PSA increased from 0.10 to 0.36 ng/mL. Six men (6.1%) met criteria for biochemical recurrence.
Hashimoto et al. 2016 [108]	12	AS	24	3 + 3	3.3 / 4.2	203/517	2 out of 10 patients Gleason score upgrade on follow-up biopsy.
Kacker et al. 2016 [94]	28	AS	38.9	3 and 4	3.29	328 / 469	Biopsy progression in men on AS was unaffected by TTh over 3

							years, compared to men on AS who did not get TTh. During TTh and AS, PSA increased by 1.04 ng/mL, although this did not reach statistical significance.
Ory et al. 2016 [109]	82	RP EBRT HIFU AS	41	6 (32) 7 (39) 8 (7) 9 (4)	RP: undetectable before / after TTh EBRT: 0.125 / 0.18	182 / 381	No patients were upgraded to higher Gleason score on subsequent biopsies. No biochemical recurrence in men treated with RP. 3 men (6%) treated with EBRT had biochemical recurrence. PSA velocity 0.001, 0.12 and 1.1 µg/L per year in the RP, EBRT and AS groups, respectively.

RP = radical prostatectomy; BT = brachytherapy; EBRT = external beam radiation therapy; HIFU = high intensity focused ultrasound; PT = proton therapy; ADT = androgen deprivation therapy; AS = active surveillance; WW= watchful waiting.

** SEER-Medicare data categorizes differentiation pattern (well, moderate, poor) rather than Gleason score.

* Follow-up period from the initiation of testosterone therapy.

Adapted from Kaplan et al. [110]

Table 2: Expert recommendations for managing TD in men with active or treated PCa.

Prior to initiating testosterone therapy Candidates for TTh should have a diagnosis of testosterone deficiency based on clinical history and laboratory diagnosis. Patients must be made aware that safety data are limited and the degree of risk of PCa progression or recurrence is unknown. Confirm there are no medical contraindications (eg, erythrocytosis) to testosterone therapy. PSA should be undetectable or <0.1 ng/mL following radical prostatectomy, or stable following radiation treatment. The most suitable candidates are those with low-risk disease with apparent cure at least one year following PCa treatment. Men with moderate- or high-risk disease, or those on active surveillance should be advised that they are at risk for cancer recurrence or progression, even without TTh. Should recurrence or progression occur, it is unknown to what extent TTh may have contributed to this outcome. The clinician should use shared decision-making and obtain informed consent. Patients should be advised that PSA may rise with TTh, particularly if baseline serum T is below the saturation point, ie, 250ng/dL. A new PSA plateau will be achieved at 3-6 months. If PSA continues to rise after 6 months, this may indicate disease progression and appropriate investigative steps should be taken.
Suitable options for testosterone therapy Short-acting formulations are preferred for initial treatment. Longer-acting formulations such as intramuscular testosterone undecanoate or subcutaneous pellets may be considered once PSA is stable.
Following initiation of testosterone therapy Measure hematocrit and/or hemoglobin 2–4 times in the 1st year, then at least 1-2 times annually. Measure PSA every 3–4 month in the 1st year after initiating testosterone and at least twice a year thereafter. Perform DRE 1–2 times within 1st year, then annually. Men on active surveillance should undergo prostate biopsy annually for the first two years, and if no progression is noted, may then follow standard AS protocols.

Adapted from Kaplan AL, Hu JC, Morgentaler A, Mulhall JP, Schulman CC, Montorsi F. Testosterone Therapy in Men With Prostate Cancer. *Eur Urol.* 2016;69(5):894-903.