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Case Report

Testosterone Replacement Therapy in Men with Prostate Cancer

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Abstract

Ever since Hodges and Huggins demonstrated the androgen-sensitive nature of prostate cancer in 1941, the Urologic community has accepted the dogma that testosterone replacement therapy (TRT) leads to the development or progression of prostate cancer. Contemporary evidence fails to demonstrate a causative link, however, which has important implications for the 2-6% of men who suffer from late onset hypogonadism (LOH). Furthermore, while a few well-publicized studies have vilified TRT for its cardiovascular toxicity, multiple other studies report myriad physical, metabolic, and cognitive benefits, as well as improved overall survival. The 20% of men who experience LOH after definitive treatment for prostate cancer, as well as the growing cohorts of men with low- and intermediate-risk prostate cancer on active surveillance, will surely benefit from further investigation into the domain of TRT and prostate cancer. This review will focus on contemporary evidence and professional society guidelines for the use of TRT in such patients.

INTRODUCTION

Several recent studies have endorsed testosterone replacement therapy (TRT) in elderly men with symptomatic hypogonadism, demonstrating beneficial effects in domains of sexual function, physical function, and mood [1], increased bone density, reduced fat mass [2], and improved glycemic control [3]. There are even retrospective reports of improved overall survival for hypogonadalmen treated with testosterone [4-6]. These benefits are tempered by other studies purporting increased rates of cardiovascular events [7,8], although these studies were limited by including debilitated patients who were treated with supraphysiologic doses of testosterone. There is thus considerable controversy within the field regarding TRT, vis-à-vis indications and contraindications for treatment. Furthermore, additional toxicities such as polycythemia, infertility, peripheral edema, exacerbation of pulmonary edema and congestive heart failure must also be considered [9,10].

Ever since Hodges and Huggins demonstrated the androgen-sensitive nature of prostate cancer in 1941 [11,12], Urologists have dogmatically accepted a theoretical risk of exacerbation of lower urinary tract symptoms (LUTS) from benign prostatic hyperplasia (BPH) with the administration of exogenous testosterone, as well as a putative increased risk of prostate cancer—both de novo and progression of occult cancer [13]. Although castration, surgical or pharmacologic, indeed induces regression of prostate cancer, and some evidence exists for metastatic cancer progression in castrated men who are given supplemental testosterone [11], the definitive link between testosterone administration and (1) de novo incidence of prostate cancer, (2) progression of pre-existing prostate cancer and (3) biochemical recurrence (BCR) after definitive therapy has not been established. Several recent papers have examined the association between TRT and prostate cancer with important implications for TRT in elderly hypogonadal men with (1) abnormal digital rectal exam (DRE), (2) history of treated prostate cancer and (3) current prostate cancer on active surveillance. This review will focus on contemporary evidence and professional society guidelines for the use of TRT in these patients.

Epidemiology of Hypogonadism

About 40% of men between 40-70yo have serum testosterone levels <300ng/dL [14], while only 2-6% are symptomatic [15,16]. Symptoms of hypogonadism include lethargy, fatigue, impairment in concentration or memory, depression, reduced libido, and erectile dysfunction [17]. Further morbidity and even mortality implications of hypogonadism have been explored by several studies. Indeed, hypogonadism has been associated with several components of the metabolic syndrome, including impaired glucose tolerance, dyslipidemia, obesity, and osteopenia/osteoporosis [18]. Conversely, men treated with TRT have been shown to have improved survival in retrospective studies. A Veterans Administration study of n=398 men with serum testosterone <250ng/dL treated with testosterone for mean 20.2 months had half the mortality rate (10.3% vs. 20.7%) at mean follow-up of 40.5 months compared to n=633 untreated

men [5]. Another study of n=581 men with type 2 diabetes demonstrated similar results when comparing men treated with TRT and followed for mean 5.81 years (mortality 9% in TRT group vs. 17.2% non-TRT group) [6]. Thus, despite the controversy the potential for clinical benefits to TRT mandates a critical appraisal of selection criteria for this therapy—which have traditionally excluded men with BPH and prostate cancer.

Androgen Physiology and Prostate Growth

During embryologic development androgen is required for the epithelial budding off of the urogenital sinus that initiates prostate development, as evidenced by animal studies with mouse models [19]. Thus prostate growth is an androgen-dependent phenomenon. Under normal physiologic conditions in the adult male, Leydig cells of the testis are stimulated by gonadotropins (i.e. luteinizing hormone) to synthesize testosterone. Testosterone serves as a pro-hormone that is converted into hihydrotestosterone (DHT) by the 5α-reductase enzyme in the prostate. Inhibition of the type 2 isoform of this enzyme is achieved by finasteride, which is shown to reduce prostate volume by ~25%, and demonstrates the androgen-dependency of prostate epithelium—dutasteride inhibits both isoforms of the 5α-reductase enzyme [20]. While testosterone is the major circulating androgen, DHT has a five-fold higher concentration in the prostate, and is the prime regulator of prostatic cellular growth, differentiation and function [21]. On the cellular level, free testosterone diffuses into the epithelial cell and binds to androgen receptors in the cytoplasm, dimerizes, and translocates to the nucleus. The resulting activated receptor/coactivator complex binds to androgen response elements—specific short sequences of DNA—that then act as transcription factors for the production of mRNA and ultimately proteins (i.e. PSA or prostatic acid phosphatase). Interestingly, the gene expression analysis by Schaeffer et al., of the murine prostate rudiment at three time points during the first 48 hours of androgen exposure revealed expression of genes previously implicated in prostate carcinogenesis: phosphatase and tensin homolog (PTEN), fibroblast growth factor (FGF)/mitogen-activated protein kinase (MAPK), and Wnt [19].

Impact of TRT on serum and intraprostatic PSA and androgen levels

Concern for exacerbation of BPH-related symptoms or progression of prostate cancer has traditionally influenced recommendations for avoiding TRT in at risk patients. Indeed, previously reported contraindications to TRT by The Endocrine Society have been abnormal DRE, American Urological Association Symptom Score (AUASS) >19, and prostate specific antigen (PSA) >4ng/mL or >3ng/mL in African American men or those with first-degree relatives with prostate cancer [22]. As early as 1840, Hunter demonstrated that prostatic epithelium undergoes atrophy after castration [23]. The physiologic impact of exogenous testosterone administration may not be so straightforward, however, as multiple studies have shown that while serum testosterone levels rise, intraprostatic levels are not altered. In 2006, Marks et al., conducted a randomized controlled trial of n=44 healthy volunteers with late-onset hypogonadism (LOH) who underwent baseline 12-core transrectal ultrasound-guided (TRUS) prostate biopsy and were then randomized to biweekly testosterone enanthate 150mg IM vs. placebo for 6 months [24]. TRUS biopsy was repeated after the treatment phase. Serum total and free testosterone levels increased in the experimental group only (from 282 to 640ng/dL, and 48 to 162pg/mL, respectively), while prostate tissue levels of both testosterone and dihydrotestosterone (DHT, the principle active metabolite of testosterone produced by the enzyme 5-alpha reductase) were unchanged in both groups (Figure 1). Serum PSA levels increased in the treatment group, as did serum hematocrit, although a significant increase in serum PSA was also observed in the placebo group. The incidence of prostate cancer (9.5% vs. 10.5%) and high grade prostatic intraepithelial neoplasia was not changed in the experimental group, although there was a trend toward greater atrophy score [24]. Therefore, short duration exogenous testosterone did not increase intraprostatic androgen concentrations or contribute to a higher incidence of prostate cancer.

The impact of TRT on serum PSA has been examined in a recent meta-analysis of 15 studies including n=739 patients who received TRT for 3-12 months vs. n=385 control patients [25]. In the nine studies that had complete PSA information, the TRT groups had higher PSA levels after treatment (mean 0.154 higher). Substratification by mode of administration revealed no change in PSA level after transdermal TRT compared to control groups (0.085), while this difference was significantly greater for patients receiving intramuscular testosterone (0.271) (Figure 2) [25]. Similarly, of the three studies that reported on the development of prostate cancer, there was no increased incidence after TRT.

The Impact of TRT on BPH

The impact of TRT on prostate growth and lower urinary tract symptoms is also controversial. The randomized study by Marks

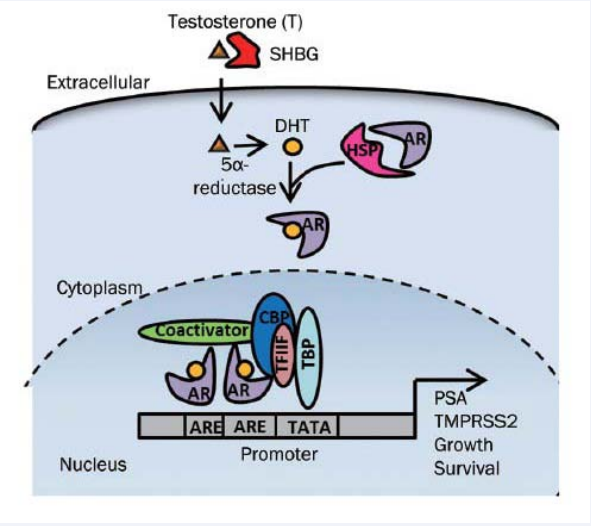

Figure 1 Serum levels of testosterone and dihydrotestosterone (DHT) increased after 6 months of testosterone replacement therapy (TRT). Prostate tissue levels of androgens did not change significantly. Boxes contain 50% of data; horizontal line represents median value, whiskers contain 100% of data. Statistical outliers denoted by asterisks [24].

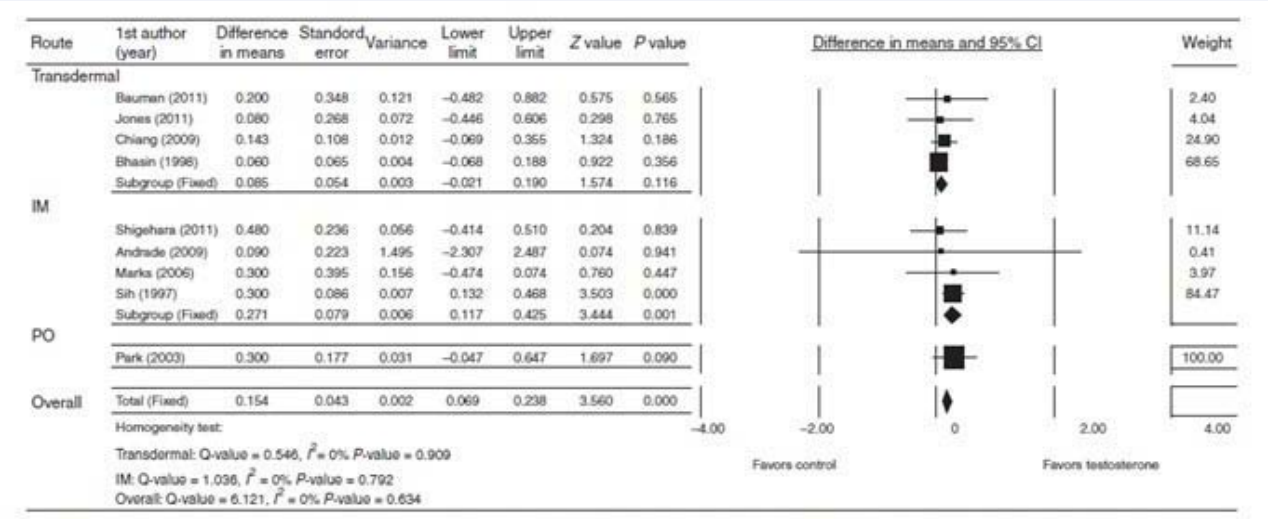

Figure 2 Forest plot comparing change in PSA level by mode of testosterone administration: transdermal, intramuscular (IM), and oral (PO). CI = Confidence Interval, bounds represent 95% CI [25].

et al., showed no change in prostate volume after 6mos of TRT compared to placebo [24]. Studies on longer durations of TRT in men with BPH actually report improvement in BPH symptoms. The etiology of this seeming paradox lies in the presence of the androgen receptor in urothelium, bladder, urethra, and prostate, and the putative loss of tissue elasticity and onset of bladder fibrosis in the hypogonadal state [26]. A randomized, controlled trial by Shigehara et al., examined 52 hypogonadal men with BPH randomized to 12 months of TRT vs. placebo [27]. International Prostate Symptom Scores (IPSS) were significantly decreased in the TRT group only, without any change in post-void residual measurements in either group. Similar results were reported by Kalinchecko et al., without any increase in prostate volume after TRT [28]. Furthermore, studies of TRT to achieve supraphysiologic testosterone concentrations in younger, healthy men demonstrate no change in prostate volume or even serum PSA levels after 10-15 weeks of therapy [29,30]. These studies are admittedly limited by short duration of treatment.

Retrospective evidence for improvement in voiding parameters after much longer durations of testosterone use (mean 57.1 months) comes from a series of n=262 men with LOH [31]. The authors sought to determine how obesity and LUTS changed after interruption of TRT (for mean 16.9 months) and subsequent reinstatement of TRT (for mean 14.5 months). In men on continuous TRT during the study interval (mean 96.9 months), prostate volume increased from mean 33mL to 34mL, and PSA remained stable (1.3ng/mL to 1.4ng/mL). Furthermore, IPSS decreased from 6.1 to 5.7, PVR decreased from 14.5mL to 13.3mL, and International Index of Erectile Function (IIEF) scores remained stable as well. These parameters were significantly worsened in the TRT withdrawal group, and subsequently improved upon TRT reinitiation. Notably, in the TRT interruption group PSA levels declined from 1.9ng/mL to 1.4ng/mL, and then rose to 1.6ng/mL after reinstatement of TRT.

Therefore, exogenous testosterone does not appear to exacerbate BPH-related lower urinary tract symptoms, but has been shown by both retrospective and level one evidence to offer improvement.

Saturation Model

In 1941, Hodges & Huggins reported on n=21 patients with locally advanced or metastatic prostate cancer who experienced weight gain, resolution of anemia, and improvement of bone pain after surgical castration [11]. This discovery led to the Nobel Prize in Medicine or Physiology in 1966 for demonstration of the androgen-sensitive nature of prostate cancer. This seminal work contributed to the specious dogma that testosterone underlies the development of prostate cancer. While Huggins & Hodges reported that testosterone administration in castrate men with metastatic prostate cancer resulted in increased acid phosphatase levels after two weeks [11], Prout and Brewer reported rapid progression or death in ~50% of castrated men who received T [32], such findings are confined to men already in a castrate state. Hormonally-intact men in these studies did not experience prostate cancer progression [33], Such reexamination of the evidence led Morgentaler to develop the "Saturation Model" in 2007, which states that prostate cancer is sensitive to changes in serum androgens only at very low concentrations, but relatively insensitive above a threshold saturation point (i.e. the concentration of maximal androgen stimulation) (Figure 3a&3b) [33-35].

This model is reinforced by the observations that 1. serum PSA levels do not correlate with serum testosterone concentrations in the general population [36], 2.administration of 5-alpha reductase inhibitors reduces serum PSA levels [37] and 3.supraphysiologic TRT to healthy men for up to 9 months does not result in significantly increased PSA levels or prostate volume [29,30]. Furthermore, *in vitro* studies have reported maximal binding of testosterone to the androgen receptor at a concentration of ~125ng/dL [38]. The fact that this concentration is twice this value *in vivo* is explained by the binding of 50% of circulating testosterone to sex hormone binding globulin [35,39]. The

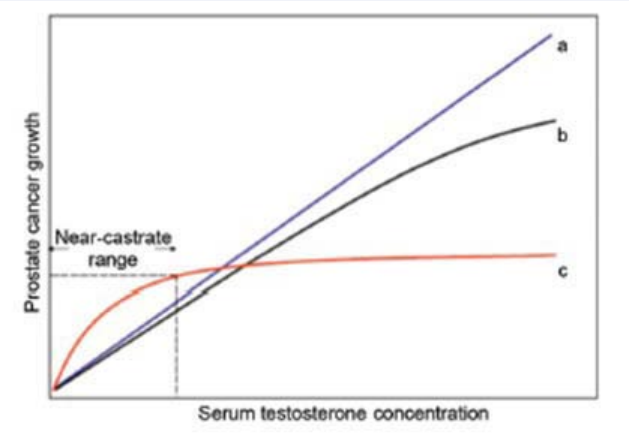

Figure 3a Saturation model for prostate cancer growth and serum testosterone concentration (curve "c"). Curves "a" and "b" represent the traditional dogma [34].

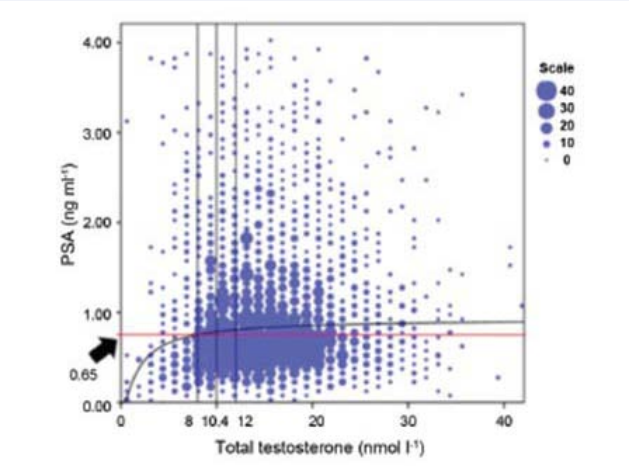

Figure 3b Saturation curve of serum prostate specific antigen (PSA) and serum testosterone level as reported by Rastrelli et al in a series of n=2967 men. The saturation point occurs at 250ng/dL [33].

saturation point has been demonstrated to be at approximately 250ng/dL, based on a study of n=2967 men by Rastrelli et al., which examined baseline serum PSA and testosterone levels [35]. The examiners found declining PSA levels below testosterone concentration of 250ng/dL, but relatively stable PSA levels at testosterone concentrations above this threshold (Figure 3b) [35]. Morgentaler & Connors accordingly describe the impact of testosterone on prostate cancer growth "'like water for a thirsty tumor.' The critical distinction is that once thirst is quenched, additional water serves only as excess" [33].

Impact of TRT on prostate cancer incidence in longitudinal population studies

Multiple longitudinal studies have revealed no correlation between endogenous testosterone levels and a man's risk of developing prostate cancer [40,41]. There is some evidence, however, that low serum testosterone correlates with higher risk of positive prostate biopsy [42,43]. Testosterone deficiency has also been associated with increased D'Amico risk category, higher Gleason score, higher pathologic stage [44], risk of seminal vesical invasion [45], and even higher rate of biochemical recurrence [44].

Regarding the impact of TRT on risk of prostate cancer, a recent systematic review and meta-analysis by Cui et al., analyzed 22 randomized controlled trials comprising n=2351 patients [46]. Route of administration of TRT was noted (i.e. injection, transdermal, oral) and duration of therapy was stratified into short-term (<12 months) and long-term (12-36 months). The investigators were unable to find a statistically significant association between TRT and the reported outcomes of prostate cancer, prostate biopsy, and detection of prostate nodule (Figure 4a&4b) [46]. Similarly, Baillargeon et al., reported a series of 52,579 men from the SEER database and showed that patients who underwent TRT (for various durations) had similar risk for high-grade prostate cancer compared to untreated men [47]. The longest published experience comes from a combined series from three prospective registries totaling 1,023 men with symptomatic hypogonadism and serum testosterone level <350ng/dL treated for median 5 years [48]. Although this study did not include a control group of patients, the incidence of prostate cancer of 1.08% compared favorably to the incidence presented in the Prostate, Lung, Colon, and Ovarian Cancer (PLCO) Trial and the European Randomized Study for the Screening of Prostate Cancer (ERSPC): 7.35% and 9.6%, respectively [49, 50]. TRT was therefore not associated with higher risk of prostate cancer [48]. Admittedly, studies with much longer follow-up are required and the incidence of prostate cancer diagnosis should be revisited as these registries mature.

Impact of TRT on treated PCa

Hypogonadism has been reported in over 20% of men after radical prostatectomy [51]. This is a substantial population of men who may benefit from TRT, but who have been traditionally excluded from this therapy by prior dogma. Multiple retrospective studies have examined the impact of TRT on BCR rates after definitive treatment, including radiation therapy (XRT) [52], brachytherapy [53,54] and radical prostatectomy (RP) [55]. These studies are limited by small sample sizes and relatively short follow-up times, but suggest the safety of TRT in this population. Khera et al., published a recent review of studies examining TRT and prostate cancer, both for treated disease and for men on active surveillance (Figure 5) [17]. Kaufman &Graydon reported the longest follow-up of 12 years for n=7 men who received TRT after RP and demonstrated no recurrence [56]. The largest series by Pastuszak et al., examined n=103 men with prostate cancer (25% high-risk) treated with radical prostatectomy who were later treated with TRT for LOH [55]. Compared to n=49 eugonadal control patients (31% high-risk), biochemical recurrence rates at median 27.5 months follow-up were 4% in the TRT group versus 16% in the non-TRT group (non-significant).

Impact of TRT for men on active surveillance for PCa

The evidence for men on active surveillance for prostate cancer is also largely retrospective. Initial studies in this domain included small cohorts of men with limited follow-up.

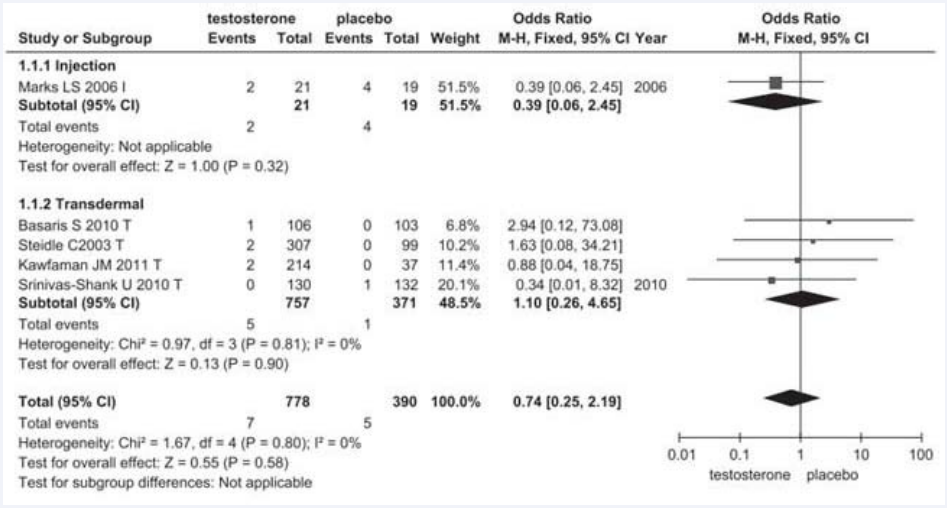

Figure 4a Meta-analysis Forest plot demonstrating changes in prostate cancer incidence in longitudinal studies of testosterone replacement therapy, organized by route of administration [46].

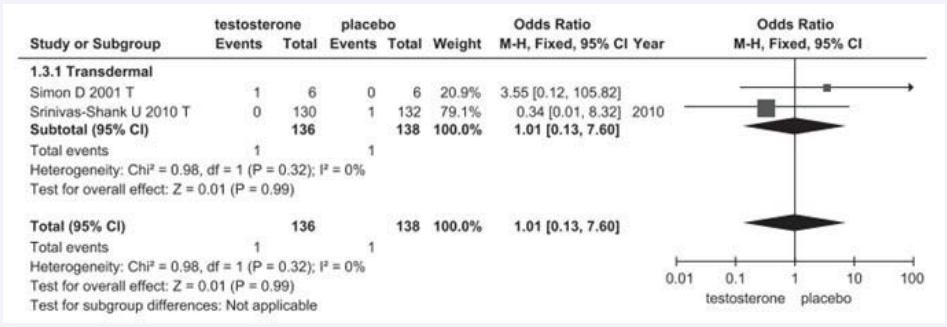

Figure 4b Meta-analysis Forest plot demonstrating changes in the incidence of prostate nodule in longitudinal studies of testosterone replacement therapy [46].

Study	No. of patients	Intervention	Follow-up, mo.	Gleason score (no. of patients)	Pretreatment PSA	Post-treatment PSA	Pretreatment testosterone, ng/dL	Post-treatment testosterone, ng/dL	Comments
Agarwal et al. (61)	10	RP	19	6 (2) 7 (7) 8 (1)	<0.1	<0.1	197	591	No PSA recurrences
Kaufman et al. (56)	7	RP	24	6 (6) 7 (1)	<0.1	<0.1	97	434	No PSA recurrences; longest follow-up = 12 yr
Khera et al. (17)	57	RP	13	≤6 (24) 7 (26) 8 (4)	0.005	0.005	255	459	No PSA recurrences
Pastuszak et al. (55)	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 testosterone therapy; four PSA recurrences in the testosterone therapy group (4%), eight recurrences in the comparison group (16%)
Sarosdy (54)	31	Brachytherapy	60	5 (3) 6 (19) 7 (6) 8/9 (3)	NA	<1	188	489	No PSA recurrences
Morales et al. (62)	5	EBRT	14.5	6 (2) 7 (1) 8 (2)	0.1–0.97	<0.1–1.08	150 (5.2 nmol/l)	507 (17.6 nmol/l)	One patient had a transitory increase in PSA; none had PSA increase >1.5 ng/ml
Pastuszak et al. (52)	13	Brachytherapy and EBRT	29.7	6 (4) 7 (7) 8 (2)	0.30	0.66	178	368	No PSA recurrences
Morgentaler et al. (57)	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
Morales et al. (63)	6	AS	NA	6 (5) 8 (1)	5.66	NA	259 (9 nmol/l)	NA	Variable PSA response in several men; no follow-up biopsies reported; one man subsequently underwent RP

Figure 5 Results of testosterone replacement therapy in men with prostate cancer. PSA = Prostate-Specific Antigen; RP = Radical Prostatectomy; PCa = Prostate Cancer; NA = Not Available; EBRT = External-Beam Radiation Therapy; AS = Active Surveillance [17].

Criteria to consider before initiating testosterone therapy in men with history of treated prostate cancer
The clinical picture is consistent with a diagnosis of testosterone deficiency.
The patient must understand that safety data are limited and that there is an unknown degree of risk of PCa progression or recurrence.
The patient must be willing and able to provide informed consent.
No medical contraindications to testosterone therapy (eg, erythrocytosis) exist.
There is an undetectable or stable PSA level.
Clinicians must be prepared for the possibility of PCa recurrence or progression, which will occur in some men regardless of testosterone therapy but may be attributed to testosterone therapy by patients, family, or other clinicians.
Use testosterone therapy with extreme caution in men at high risk for PCa recurrence or progression.
Do not recommend testosterone therapy for men currently receiving any form of ADT.

Figure 6 PCa = Prostate Cancer; PSA = Prostate-Specific Antigen; ADT = Androgen-Deprivation therapy [17].

Morgentaler et al., published a retrospective review in 2010 of n=14men with prostate cancer on active surveillance who elected to receive TRT [57]. After mean duration of 23.5 months, at planned repeat prostate biopsy 7% of patients demonstrated progression to intermediate risk disease (Gleason 4+3=7), without significant change in serum PSA. Of note, all patients in this study had Gleason 6 prostate cancer. More recently, Kacker et al., examined progression while on active surveillance for n=28 men with hypogonadism treated with TRT compared to n=96 untreated men [58]. There was no difference in rates of progression to treatment after 40.5 months follow-up in this retrospective study. The inclusion criteria for this study were broader, as they allowed Gleason3+4=7 patients (~20% of the AS cohort). This series is the largest cohort to date investigating TRT in men on active surveillance, and thus further studies are needed.

Society recommendations

Several professional organizations have included provisions on prostate cancer patients in their guidelines for the treatment of male hypogonadism.

The European Association of Urology Guidelines on Male Hypogonadism corroborates the evidence presented in this review, citing the lack of level 1 evidence [59]. TRT is contraindicated in men with advanced prostate cancer, but reasonable for men treated with radical prostatectomy or brachytherapy and no evidence of disease recurrence. The guideline states that:

"Symptomatic hypogonadal men who have been surgical treated for localized prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis) can be cautiously considered for a TRT. In these men treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score <8; pathological stage pT1-2; preoperative PSA <10ng/mL). Therapy should not start before one year of follow-up after surgery and patients should be without PSA recurrence."

The American Urological Association has issued a Position Statement that "current evidence does not provide any definitive answers regarding the risks of testosterone therapy on prostate cancer and cardiovascular disease, and patients should be so informed" [60].

The Endocrine Society last convened a task force for the development of clinical guidelines in 2010 and advised "against testosterone therapy in patients with breast or prostate cancer." The lack of data from randomized trials "precludes a general recommendation," although patients "who have undergone radical prostatectomy and have been disease-free 2 or more years after radical prostatectomy and who have undetectable PSA levels may be considered for testosterone replacement on an individualized basis" [22].

A recent review by Khera et al., has proposed several criteria to consider prior to initiation of TRT in men with history of treated prostate cancer (Figure 6) [17].

FUTURE DIRECTIONS

There is a clear need for further investigation in this domain. Contemporary randomized, controlled trials investigating active surveillance should adopt parallel objectives to monitor testosterone levels and identify patients who would benefit from treatment of hypogonadism. Even without formal TRT (as this may be a valid exclusion criteria to participation in current AS studies) identification of any correlation between baseline testosterone levels and risk of upgrading/upstaging during AS and progression to definitive treatment would be informative. The single randomized, placebo-controlled study investigating TRT after treatment for prostate cancer (Baylor College of Medicine, Clinicaltrials.gov identifier NCT00848497) was closed after 6 years for failure to enroll patients. Indeed, further randomized, controlled studies are needed to further elucidate the role of TRT after treatment for prostate cancer. Guidance for TRT in such patients may come from professional societies, which must update their Guidelines and Best Practice Statements to reflect contemporary evidence.

CONCLUSIONS

The dogmatic contraindication to testosterone replacement therapy for men with history of treated prostate cancer and even men with prostate cancer on active surveillance has been recently challenged by contemporary evidence. While further randomized studies are required to further elucidate the role of TRT in this population of men, it should not be vilified by the Urologic community. Indeed, after proper patient selection (based on D'Amico risk category and lack of concurrent androgen deprivation therapy) and thorough patient counseling, TRT may be offered to men with symptomatic hypogonadism to foster clinical improvement in multiple physical, cognitive, and functional domains. The ability of TRT to offer an overall survival benefit without risk of disease recurrence to this population

of prostate cancer patients—as has been reported in other populations of elderly men—shows promise but surely requires further investigation.

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