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Updated Review of Testosterone Replacement Therapy in the Setting of Prostate Cancer

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Abstract

Since the 1940s, elevated serum testosterone (T) levels have been infamously suggested as a causal factor in the development of prostate cancer (PCa); this time was also the dawn of both surgically and pharmacologically induced castration. However, men suffering from primary or secondary hypogonadism and who are concomitantly paradoxically at risk for developing PCa cited the adverse effects of T deficiency. In the past 25 years, researchers have published on the genetic, biochemical, and clinical outcomes of testosterone replacement therapy (TRT) in hypogonadal men. The longstanding dogma of the deleterious effects of TRT has recently been challenged, and it now appears that TRT may have an important therapeutic role in the treatment of hypogonadism in those men with either low-risk, active, or previously treated PCa. This review summarizes the latest findings on the treatment of hypogonadal men with a history of PCa, emphasizing results of clinical research studies.

Keywords: testosterone; PCa; hypogonadism; androgen treatment

Introduction

Prostate cancer (PCa) is the most common cancer in men in the United States, with ~192,000 new cases in 2020.[1] This number of annual cases is expected to rise as the population ages. For patients deemed to have low-risk PCa, active surveillance (AS) is an accepted treatment option.[2–5] In cases that require treatment, surgery, radiation therapy, high-intensity focused ultrasound (HIFU), and cryotherapy are available options.

Even after successful treatment, biochemical recurrence (BCR) of PCa has been cited at a rate of 13–53% in patients after radiation therapy[6] and at 30.2% 3 years post–radical prostatectomy (RP).[7] It is estimated that up to 30% of males between 40 and 79 years of age are hypogonadal and 39% of males between the ages of 45–85 have a testosterone (T) level <300 ng/dL.[8,9] Hence, it is not uncommon for PCa patients to also be diagnosed with T deficiency at any stage in their disease, whether it is before treatment, after cure, in those who have BCR, or in those who are on AS. Low T levels have been studied regarding their potential to increase the risk of PCa complications in diagnosed men, including higher incidence of extraprostatic metastasis,[10] seminal vesicle invasion,[11] and increased positive surgical margins.[12]

Irrespective of PCa, hypogonadal men treated with testosterone replacement therapy (TRT) experience clinical benefits through increased muscle mass, bone density, mood, and sexual health/performance.[13] Normalization of T levels is also postulated to potentially lower cardiovascular disease risk by reducing cholesterol levels, ameliorating glucose metabolism, and lessening the risk of metabolic syndrome.[14] Potential side effects of TRT include polycythemia, gynecomastia, BPH, and lowered HDL cholesterol.

The exact nature of the relationship between androgens and PCa is a particularly relevant topic given that PCa mortality has decreased by ~50% in the past two decades, resulting in a significant increase in PCa survivors with potential for experiencing symptoms

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of hypogonadism.[15] In this communication, the available evidence on the safety of TRT in men at risk for or with a previous or current diagnosis of PCa is reviewed.

Androgen Receptors and the Prostate

In the 1940s, Huggins and Hodgkins established a connection between androgenic hormones and PCa, laying the foundation for ADT in the treatment of PCa. They suggested that exogenous T would lead to increased cancer recurrence, measured by prostatic acid phosphatase (PAP) levels. This conclusion was based on the results of a very small study of three PCa patients who experienced a rise in PAP levels on administration of T injections, which was followed by a subsequent drop in enzyme levels after cessation of treatment. PAP has since been observed to be much less reliable than prostate-specific antigen (PSA) in the diagnosis of PCa (45% sensitivity for PAP vs. 96% for PSA) and in monitoring disease recurrence (25% of patients with metastatic disease presented with normal PAP levels[16,17]).

In 1996, Morgentaler et al. observed a high prevalence of PCa confirmed by biopsy in men with low total or free T levels, regardless of normal PSA levels.[18] Ten years later, Morgentaler and Rhoden documented additional results wherein, in 345 hypogonadal men with a PSA of ≤4.0 ng/mL, PCa was detected in 21% of men with T levels ≤250 ng/mL,[19] compared with 12% of men with a T level >250 ng/mL.

Morgentaler and Traish have proposed a saturation model to describe the varying sensitivity of the androgen receptor (AR) to either physiologically low or high T concentrations. They postulate that maximum AR activity is achieved at low T concentrations and saturation is responsible for less AR activity at higher T concentrations.[20] In human prostatic tissue, the AR is reported to become saturated and unreceptive to further increases in activity at T concentrations of 120 ng/dL *in vitro* and 240 ng/dL *in vivo*.[21,22] Separately, Rastrelli et al. identified the T AR saturation at a concentration of ∼8 nmol/L (231 ng/dL).[23]

In one study, healthy men injected with 250 and 500 mg T per week had prostate volumes measured after 15 weeks. Despite significant elevations in free and total T, no increase in PSA or prostate volume was observed, thereby supporting the androgen saturation theory.[24] A randomized, double blind, placebo-controlled study also concluded that a 6-month TRT trial did not cause a significant increase in prostate tissue androgen concentrations.[25] The T saturation model also has interesting implications in the development of castration-resistant prostate cancer (CRPC). It has been postulated that supraphysiologic androgen levels may even paradoxically inhibit the growth of AR expressing human PCa cells, and similar antitumor activity has been observed in breast cancer patients exposed to high concentrations of estrogen.[26]

TRT and Risk of Developing PCa

Researchers have evaluated whether TRT increases the risk of developing newly diagnosed PCa. We review several pertinent studies with large sample sizes and new data in this section. Although many of these reports are limited by their study design, variability of inclusion criteria, and uncertainty regarding the length of TRT, and although the RCTs have reported data with mean and median follow-up less than 5 years, it appears that TRT is safe and does not increase the incidence of PCa.

A UK-based retrospective database review published in 2019 identified 12,779 patients with "late-onset hypogonadism.[27]" The mean follow-up period was 4.6 years, though 37.3% and 9.2% of patients received follow-up for at least 5 and 10 years, respectively. The use of TRT in that population did not result in increased risk of PCa (hazard ratio [HR] = 0.97 [95% confidence interval; CI 0.71–1.32) in an overall analysis, nor when propensity score matching was applied (HR = 0.87, 95% CI 0.56–1.36).[27]

In another longer-term study of T therapy in 1023 hypogonadal men, with a mean follow-up of 5 years, there were 11 cases of PCa (1.08%)—a prevalence figure lower than that reported by two large screening studies—the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (7.35%) and the European Randomized Study of Screening for PCa (ERSPC) (9.6%). An important limitation of this study was that younger men were included, unlike the PLCO and ERSPC trials.[28]

In a case–control study in the United States, using a Surveillance, Epidemiology and End Results (SEER) Medicare-linked database, patients with a diagnosis of PCa and with history of T use (574 men) were compared with PCa patients without history of T use (51,945). Those patients who had received TRT in the 5 years before diagnosis were found not to have an increased risk of high-grade disease at diagnosis (odds ratio [OR] 0.84, 95% CI 0.67–1.05). A multivariable analysis to assess a dose–response association among T users also did not reveal any correlation (OR 1.00, 95% CI 0.99–1.01).[29]

Another retrospective study evaluated 247 patients in Texas who commenced T therapy for a mean follow-up period of 6.5 years and compared them with 211 patients who did not receive TRT. By the end of the study, 47 men developed cancer: 27 (12.8%) not on TRT and 20 (8.1%) on TRT. No significant difference in PCa risk was found to be associated with TRT (HR 1.2, 95% CI 0.54–2.50).

In a similar report, from Sweden, Loeb et al. reported the results of a nested case–control study using the National PCa Registry of Sweden. From a multivariate analysis, no significant difference was demonstrated in PCa risk in patients with TRT exposure (OR 1.03; 95% CI 0.90–1.17). The authors went on to report that patients who had received TRT were observed to have more favorable-outcome PCa (OR 1.35; 95% CI 1.16–1.56) and a lower risk of aggressive cancer (OR 0.50; 95% CI 0.37–0.67) (28447913).[30]

In their study of 776 hypogonadal men with negative PCa screening at enrollment, Zhang et al. argued that TRT may accelerate the diagnosis of occult cancer, but not affect the overall prevalence at 7-year follow-up. They studied two groups of hypogonadal men with negative PCa screenings according to the European Association of Urology (EAU) guidelines. No significant difference was observed between the TRT group and the non-TRT group in cancer incidence at the end of the study period (9/398 vs. 5/230 respectively, $p = 0.9999$), even after performing propensity score matching to account for differences in baseline characteristics, most notably age and PSA. Of note, all cases in the TRT group were diagnosed within 18 months of treatment initiation, as compared with all cases diagnosed in the non-TRT group after 24 months of enrollment.[31] The authors concluded that TRT may speed up the diagnosis of occult cancer already present at initiation of treatment, but the therapy had a protective effect from the end of their predefined latency period until the end of the study.[31] Limitations of the study included a small subject number and aggressive lab testing/screening of the treatment group. Indeed, ongoing tri-annual transrectal ultrasound and digital rectal exam could be a potential explanation for the earlier cancer diagnosis.

In a recent meta-analysis of 26 placebo-controlled trials studying the effect of TRT on PCa, there was minimal absolute change of PSA between the beginning and end of the trial (0.1 ng/mL, 95% CI −0.28 to 0.48).[32] A major limitation of this result was the short median trial duration of 196 days. The same group reviewed 11 trials to estimate the risk of PCa diagnosis while on TRT, and they concluded that there was no significant increase in risk measured by pooled OR (0.87, 95% CI 0.3–2.5). They also did not find evidence for heterogeneity or publication bias when assessing the quality of the results.[32]

In a similar analysis, data were pooled from random-controlled trials (RCTs) but divided into two groups: short-term follow-up (less than 12 months) and long-term follow-up (12–36 months). Pooling data from the RCTs with short-term follow-up did not show an increased PCa diagnosis rate, with OR of 0.39 (95% CI 0.06–2.45; P 1/4 0.32) for the study using injectable T and 1.10 (95% CI 0.26–4.65; P 1/4 0.90) for the study using transdermal T. However, these studies did find a rise in PSA with a standard mean difference of 0.52 (95% CI 0.00–1.05, $p = 0.05$) in studies using injectable T and a standard mean difference of 0.33 (95% CI 0.21–0.45, $p = 0.00001$) for studies using transdermal T. For RCTs with a longer-term follow-up, no difference in PCa diagnosis between the treatment and placebo group 0.99 (95% CI 0.24–4.02; $p = 0.99$) was determined.[33]

TRT in Patients with Untreated PCa

Several recent retrospective studies described in this sub-section have evaluated the risk associated with TRT in hypogonadal men with untreated PCa undergoing AS.[34–38] In general, these studies are limited by their retrospective design, few participants, and short follow-up periods (Table 1).

Two trials have demonstrated that a subset of men presenting with PCa had both an improvement in symptomatic hypogonadism and PCa characteristics after T administration.[39,40] Researchers from one 2009 study treated 15 PCa patients with three progressively increasing doses of transdermal T. Three patients saw a decline in PSA, though a total of 12 patients were taken off the study after possible disease progression, as evaluated through either PSA increases or findings on imaging studies.[39]

In an analysis of SEER Medicare data, Kaplan et al. estimated that, between 1991 and 2007, 0.79% (1181/149,354 men) of men received exogenous T after a PCa diagnosis. Several statistically significant findings were presented: Men on AS were noted to be less likely to receive TRT overall (6.9 vs. 5.4 events per 100-person years, $p = 0.0001$), and cancer-related mortality was higher in the non-TRT groups when compared with the TRT group (1.6 vs. 0.9 events per 100-person years, $p < 0.0001$).[41] Limitations of the study included

Table 1. Published Studies on Testosterone Replacement Therapy in Men Treated for Prostate Cancer on Active Surveillance

References	Patients	Stage/risk category	GG/Grade Group	Pre-TRT PSA median (ng/mL)	Post-TRT PSA median (ng/mL)	Median follow-up (months)	Cancer progression definition	Comments
Morgentaler[34]	1	NR	6 (1)	8.3	3.8	24	NR	Decline in PSA in man with untreated PCa who received TRT for 2 years.
Morales[35]	7	T1 (6)	6 (5); 8 (1)	4.8	NR	24	PSA >1 ng/mL quarterly or doubling within 12 months	Observational study without substantial discussion of patient follow-up after TRT. Study asserts that TRT candidates "should be willing and able to adhere to a strict follow-up (quarterly for the first 2 years and bi-annually thereafter if they are stable)."
Morgentaler et al.[36]	13	NR	6 (12) 7 (1)	5.0 (mean)	3.6 (mean)	30	NR	Researchers concluded that TRT in patients with untreated PCa was not associated with PCa progression in the short to medium term—citing consistency with the saturation model—or maximal PCa growth at low androgen concentrations.
Kacker et al.[37]	28	NR	6 (22) 7 (6)	• 3.21 (3+3 GG TRT cohort) • 2.58 (3+4 GG TRT cohort) • 4.46 (no TRT cohort)	• 1.04 (3+3 group increase) • 0.54 (3+4 group increase) • 0.22 (no TRT group increase)	42.9	Increase in GG upon biopsy	Retrospective chart review of 28 men who underwent TRT vs. 96 men on AS for PCa who did not receive TRT. Researchers concluded: "Biopsy progression rates were similar for both groups and historical controls. Biopsy progression in men on AS appears unaffected by T therapy over 3 years. Prospective placebo-controlled trials of T therapy in T-deficient men on AS should be considered given the symptomatic benefits experienced by treated men."
Ory et al.[38]	8	Low risk	6 (6)	3.9	5.2	33	Increase in GG on biopsy	No patients on AS put on TRT were observed to show clinical or pathological PCa progression. Researchers concluded: "In the absence of randomized, placebo controlled trials our study supports the hypothesis that testosterone therapy may be oncologically safe in hypogonadal men after definitive treatment or in those on active surveillance for prostate cancer."

AS, active surveillance; GG, Gleason Grade; NR, not reported; PCa, prostate cancer; PSA, prostate-specific antigen; T, testosterone; TRT, testosterone replacement therapy

only evaluating a 5-year follow-up period and potentially unreliable clinical information available in a claims-based database.

Morgentaler et al. reported the results of prostate biopsies, serum PSA, and prostate volume in 13 hypogonadal men on AS who received TRT for 6 months for untreated PCa for 2.5 years.[36] Although the men experienced a 2.8-fold increase in serum T levels (238–664 ng/dL; $p < 0.001$), there was no significant change in mean PSA (5.5 ± 6.4 at initial biopsy vs. 3.6 ± 2.6 ng/mL after TRT, $p = 0.29$). These researchers noted that all men receiving TRT also experienced symptomatic improvement in libido, sexual performance, mood, and energy.

TRT in Patients with Treated PCa

Tables 2 and 3 summarize the published series on TRT after PCa treated with RP and radiotherapy modalities, respectively.[42–49] Recent studies have confirmed that TRT after definitive treatment for localized PCa appears safe and does not lead to increased disease recurrence.

In a large cohort analysis utilizing the Veterans Affairs Informatics and Computing Infrastructure (VINCI) database, Sarkar et al. identified 69,984 men with localized PCa, of whom 28,651 underwent RP and 41,333 received radiation. Of this total number, 469 RP (1.64%) and 543 radiation (1.31%) patients received TRT with a median follow-up of almost 7 years.[50] The investigators found that comparing those men who received TRT with those who did not, there were no between-group differences in BCR, PCa-specific mortality, or overall mortality after surgery (HR: 1.07; HR: 0.72 [$p = 0.43$]; and HR: 1.11 [$p = 0.43$], respectively) or radiation (HR: 1.07; HR: 1.02 [$p = 0.95$]; and HR: 1.02 [$p = 0.86$], respectively). One strength of this study was that it pooled a large, multi-ethnic, nationwide cohort with a high prevalence of African American men (24% prostatectomy, 28% radiation).

Ahlering et al. examined the rates of BCR in 850 patients who underwent RP for localized PCa, of whom 152 (18%) were started on TRT compared with 419 (82%) proportionally matched controls. After a median follow-up of 3.5 years, BCR occurred in 11 out of 152 (7.2%) and 53 out of 419 (12.6%) patients in the TRT and control groups, respectively. In adjusted time-to-event analysis, TRT was an independent predictor of recurrence-free survival. After accounting for the Gleason grade (GG) group, pathological stage, preoperative PSA level, and calculated free T, the authors determined that patients prescribed TRT were ~54% less likely to recur (HR 0.54, 95% CI 0.292–0.997).[51] Among those men who would eventually recur, TRT appeared to delay time to recurrence by an average of 1.5 years. Importantly, this study reported that by 2 years post-RP, 96% of patients had re-gained erectile function.

Specifically regarding hypogonadal men who underwent curative treatment for high-risk PCa, Teeling et al. conducted a single-arm meta-analysis to determine the relationship between TRT and risk of BCR. In this analysis of 13 studies and 109 men, the BCR rate was 0.00% (0.00–0.05%), lower than the expected rate for high-risk PCa survivors, suggesting that T therapy may not increase BCR risk in this patient population. The authors strongly cautioned against over interpretation, seeing that the available body of evidence was of very low quality.[52]

Another meta-analysis sought to evaluate the association between TRT in nonmetastatic PCa patients after definitive local therapy and the rate of BCR. Twenty-one studies were included with an overall pooled BCR rate of 0.01 (95% CI 0.00 − 0.02), suggesting a lack of association between TRT and BCR.[53] In subgroup analyses, pooled BCR rates were 0.00% (95% CI 0.00 − 0.02) in patients treated with RP and 0.02% (95% CI 0.00 − 0.04) in patients treated with external beam radiotherapy, brachytherapy (BT), cryotherapy, or HIFU. No heterogeneity was observed among included studies or in the subgroup analyses. A meta-analysis of 21 studies of BCR of PCa in men prescribed TRT after initiation of cancer therapy revealed that TRT in the setting of definitive PCa treatment did not increase BCR risk. Although studies varied in their PSA cutoff point for BCR, the majority (13/21) used the Phoenix definition of nadir +2 ng/mL as the end point. The researchers supported their conclusions with an identified BCR rate of 0.01% after TRT.[54]

Another study monitored PCa in 13 hypogonadal men who received TRT after previous BT or external beam radiotherapy treatment between 2006 and 2011.[55] After a median follow-up time of 29.7 months, no significant increases in PSA were observed during the study period (0.16–1.35 ng/mL, $p = 0.345$), and no reported cases of BCR were reported. Pastuszak et al. also organized a multicenter study that identified 98 men diagnosed with PCa and treated with radiation therapy. While on TRT for a median follow-up of 40.8 months, the men experienced a statistically significant median rise of 211 ng/mL in T levels and a non-significant increase in PSA from 0.08 ng/mL at baseline

Table 2. Published Studies on Testosterone Replacement Therapy in Men Treated for Prostate Cancer with Radical Prostatectomy

References	Patients	Stage/Risk category	GG/Grade Group	Pretreatment PSA, mean/median (ng/mL)	Treatment	Pre-TRT PSA (ng/mL)	Post-TRT PSA (ng/mL)	Median follow-up, months	BCR definition	BCR rate
Kaufman and Graydon[42]	7	NR	6 (6), 7 (1)	5.2	RP	<0.1	<0.1	19	PSA >0.1 ng/mL	0
Agarwal et al.[54]	10	NR	6 (2), 7 (7), 8 (1)	7	RP	<0.1	<0.1	24	PSA >0.1 ng/mL	0
Nabulsi et al.[49]	22	T2 (21), >T2 (1)	≤6 (58%), 7 (32%)	5.9	RP	NR	NR	20	NR	0.05
Khera et al.[45]	57	≤T2	6 (24), 7 (26), ≥8 (4)	5.58	RP	<0.1	<0.1	13	PSA >0.1 ng/mL	0
Sathyamoorthy et al.[47]	21	High risk	≥8 (21)	NR	RP	0.003	0.01	12	NR	0.00
Matsushita et al.[48]	71	≤T2 (84%), T3a (13%), T3b (3%)	7 (Median)	4.5	RP	NR	NR	19	PSA >0.1 ng/mL	0.014
Pastuszak et al.[55]	103	Not high risk (77), high risk (26)	<6 (1), 6–7 (74), >8 (9), NR (19)	5.2	RP	0.004	NR	27.5	PSA ≥0.2 ng/mL	0.04
Ahlering et al.[51]	152	T2 (86), ≥T3 (21)	GG1 (43), GG2 (77), GG3 (23), GG4 (2), GG5 (7)	7.2	RP	<0.05	NR	42	PSA ≥0.2 ng/mL	0.072

BCR, biochemical recurrence; ; PSA, prostate-specific antigen; RP, radical prostatectomy.

Table 3. Published Studies on Testosterone Replacement Therapy in Men Treated for Prostate Cancer with Radiotherapy or Radical Prostatectomy

References	Number of patients	Stage/Risk category	GG	Pretreatment PSA, mean/median (ng/mL)	Treatment	Pre-TRT PSA (ng/mL)	Post-TRT PSA (ng/mL)	Median follow-up, months	BCR definition	BCR rate
Sarosdy[43]	31	T1b (1), T1c (20), T2a (8), T2c (2)	≤6 (22), 7 (6), ≥8 (3)	5.3	BT	5.3	<1	60	NR	0
Davila et al.[46]	20	NR	Mean Gleason 6.2 (RP), 5 (EBRT)	6.05 (RP), 3.5 (EBRT)	14 RP, 6 EBRT	0.1 (RP), 0.15 (EBRT)	0.1 (RP), 0.1 (EBRT)	12 (RP), 9 (EBRT)	NR	0
Morales et al.[44]	5	NR	6 (2), 7 (1), 8 (2)	11.96	EBRT	0.3	0.47	14.6	NR	0
Pastuszak et al.[55]	13	NCCN low (4), intermediate (7), high (2)	6 (4), 7 (7), 8 (2)	5.8	BT/EBRT	0.3	0.66	29.7	Two consecutive increases of PSA of >0.5 ng/ml	0
Ory et al.[38]	74	D'Amico low (14), intermediate (30), high (30)	6 (24), 7 (39), 8 (7), 9 (4)	NR	22 RP, 50 RT, 1 BT, 1 HIFU			48 (RP), 36.5 (RT), 9 (BT), 42 (HIFU)	PSA ≥0.2 ng/mL (RP), nadir +2 ng/mL (RT)	0.06 (RT)

BT, brachytherapy; HIFU, high-intensity focused ultrasound; NCCN, National Comprehensive Cancer Network; RT, radiotherapy.

to 0.09 ng/mL ($p = 0.05$). Six men (6.1%) experienced BCR and three of these men underwent BT before PSA levels consequently normalized.[56]

In 20 men (49–74 age range) who underwent BT for PCa (6.2 ng/mL PSA at time of diagnosis), there was a decrease in mean PSA level, from 0.7 ng/mL before TRT to 0.1 ng/mL after TRT (TRT not initiated before at least 3 months of treatment) at the time of last follow-up (median time of 31 months).[57] Patients received long-acting 1000 mg T injections and subsequent adjusted T concentration injections to meet a free T concentration >11.7 ng/dL. Another small study of five patients also identified benefits of TRT administration in hypogonadal patients following external beam radiotherapy for localized PCa. Patients began TRT once their PSA levels reached their nadir and only one patient had a transitory PSA level increase, not more than 1.5 ng/mL.[35] All men reported improvements in symptoms associated with hypogonadism.

TRT in Patients with Advanced PCa

In the setting of metastatic castration-resistant PCa (mCRPC), an emerging body of literature supports the use of supraphysiologic levels of androgens as an adjunctive therapeutic treatment. Although the exact mechanism remains under active investigation, it appears that high-dose androgen may act by inducing double-strand DNA breaks, inhibiting relicensing of DNA in cells expressing high levels of AR repressing genes in DNA repair, downregulating AR splice variants (e.g., AR-V7), and delaying restoration of damaged DNA.[26,58–62] Both continuous and intermittent administration of high-dose testosterone (HDT) has been described, with a greater body of literature available for the latter. This intermittent HDT strategy, where T levels are quickly raised to supraphysiologic levels and then brought down to near-castration levels over ~1 month, is termed bipolar androgen therapy (BAT).

Multiple recent Phase I and II studies have been conducted to investigate TRT in the CRPC setting. The first Phase I trial evaluated the effect of increasing doses of transdermal T (2.5, 5, or 7.5 mg/day) in 15 men with low-risk CRPC. The authors observed that one patient had symptomatic progression, and three patients had a decrease in PSA (maximums decrease of 43%).[39] Those men receiving the highest dose of TRT demonstrated a longer time to progression, which was not noted to be statistically significant. No grade 3 or 4 toxicities were reported apart from one patient with cardiac toxicity at week 53.

Table 4. Published Studies on Testosterone Replacement Therapy in Men with Castration-Resistant Prostate Cancer

References	Patients	Stage/risk category	GG/Grade Group	Pretreatment PSA, mean/median (ng/mL)	Post-TRT PSA (ng/mL)	Median follow-up, mo	BCR definition	Comments
Szmulewitz et al.[39]	15	CRPC, 6 of 15 patients evidence of bone metastasis	NR	11.1	NR	2	PSA >3×nadir PSA	One patient was removed from the study due to grade 4 cardiac toxicity. The majority of patients were taken off the study due to the progression of disease by either PSA ($n = 9$) criteria or for both imaging and PSA ($n = 3$) No significant improvement in QOL identified—with further QOL improvement results pending from a larger clinical trial being performed. Researchers concluded that TRT was a "feasible and well-tolerated therapy for men with early CRPC."
Morris et al.[40]	12	CRPC metastatic cancer (soft tissue and/or bone)	8 (Median)	91	NR	2	25% increase in PSA over 3 tests	One patient was removed from the study due to epidural disease—subsequently treated with radiation. Nine of 12 patients exhibited biochemical or radiographic progression. One patient exhibited $a > 50\%$ decrease in PSA from baseline measurement. Researchers concluded that "patients with CRPC can be safely treated in clinical trials using high-dose exogenous testosterone."

The second Phase I study examined 12 men with CRPC administered transdermal TRT (7.5 mg/day) for 1 week, 1 month, or until disease progression.[40] Despite the goal of reaching supraphysiologic levels of T during the study, average serum T levels were within normal limits. Although no objective responses were observed, 33% of patients had declines of PSA of at least 20% and one reached $a > 50\%$ decline in PSA (PSA50). There were no grade 3 or 4 toxicities. Results from these aforementioned Phase I studies are presented in Table 4.

Subsequently, the Phase II TRANSFORMER trial examined 30 asymptomatic mCRPC patients with disease progression on abiraterone/enzalutamide who were treated with BAT and then re-challenged with enzalutamide.[63] The study reported a 30% PSA50 response to BAT. Twenty-one patients proceeded to enzalutamide re-challenge with a 52% PSA50 response. This study appears to support the use of BAT as a means of targeting the AR in patients who have disease progression on second-line AR signaling inhibitors.

The currently ongoing RESTORE Phase II trial has enrolled 59 asymptomatic mCRPC patients with disease progression on abiraterone ($n = 29$) or enzalutamide ($n = 30$) who were then treated with BAT and re-challenged with their most recent androgen receptor-targeted therapy.[62] After BAT, the postenzalutamide cohort showed a 30% PSA50 response versus 17% PSA50 in the postabiraterone cohort, a difference that was not statistically significant. After AR targeted therapy re-challenge, PSA50 response was significantly higher in the postenzalutamide cohort (68% vs. 16%). Median progression free survival (PFS) was longer in the postenzalutamide versus postabiraterone re-challenge cohort (12.8 months vs. 8.1 months). The authors also noted that men with detectable AR-V7 mutations in circulating-tumor DNA had worse PFS (10.3 months vs. 7.1 months). From the currently reported data, BAT appears to demonstrate clinical benefit in pretreated mCRPC patients with a greater re-sensitization seen in men treated with enzalutamide compared with abiraterone and that the presence of certain splice variants such as AR-V7 may prognose a worse response to BAT.[62]

Conclusion

The TRT for patients who have a history of untreated or treated PCa remains a debated practice, given the long-established dogma that T could act as "fuel on the fire" for PCa recurrence and growth. As previously described, this paradigm has shifted since the introduction of the saturation model hypothesis. Since then, a growing body of published case series appear to support TRT in this clinical setting. Researchers currently recommend that patients be prescribed the lowest necessary T dose to achieve serum androgen normalization and then be screened at regular intervals, depending on the administration method.

The American Urological Association (AUA) TRT guidelines recognize the lack of evidence linking TRT to the development of PCa, as well as insufficient evidence to quantify a risk–benefit ratio of TRT in patients with a history of PCa.[64] As such, hypogonadal patients should make an informed consent before initiating TRT, after a thorough conversation with their provider of the risks and benefits. Until definitive evidence from long-term prospective or placebo-controlled RCTs becomes available, patients under AS, or with a history of PCa must understand the importance of strict compliance with increased T, PSA, and digital rectal exam monitoring frequency.

Currently, neither the AUA nor EAU provides guidelines on monitoring intervals for TRT patients on AS or after RP or radiation therapy. Data from available studies indicate that serum T, PSA, and digital rectal exam findings should be evaluated at least every 3–6 months, according to a physician's best judgment given a patient's goals, medical history, and perceived PCa risk.[65] For patients on AS, it has been suggested that a patient's relative risk be evaluated by a multidisciplinary medical team, including a urologist, endocrinologist, and oncologist.[66] In all cases, serum T levels should be kept as low as possible to meet a patient's replacement needs.

Future studies, in addition to focusing on specific PCa risk with TRT in populations stratified by factors such as GG group, treatment during AS, or history of prior definitive treatment for localized PCa, should also focus on providing results of quality-of-life metrics to help enumerate the risk–benefit ratio for patients when making health care decisions.

Authors' Contributions

Conception and design: W.J.G.H.; Data acquisition and analysis: M.P. and I.V.; Drafting article: M.P. and I.V.; Revising article: A.S. and W.J.G.H.; Approval: All authors.

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Abbreviations Used

AR = androgen receptor
AS = active surveillance
AUA = American Urological Association
BAT = bipolar androgen therapy
BCR = biochemical recurrence
BT = brachytherapy
CRPC = castration-resistant prostate cancer
EAU = European Association of Urology
ERSPC = European Randomized Study of Screening for PCa
HDT = high-dose testosterone
HIFU = high-intensity focused ultrasound
HR = hazard ratio
mCRPC = metastatic castration-resistant PCa
PAP = prostatic acid phosphatase
PCa = prostate cancer
PLCO = Prostate, Lung, Colorectal, and Ovarian
PSA = prostate-specific antigen
RCT = random-controlled trial
RP = radical prostatectomy
RT = radiotherapy
SEER = Surveillance, Epidemiology and End Results
T = testosterone
TRT = testosterone replacement therapy