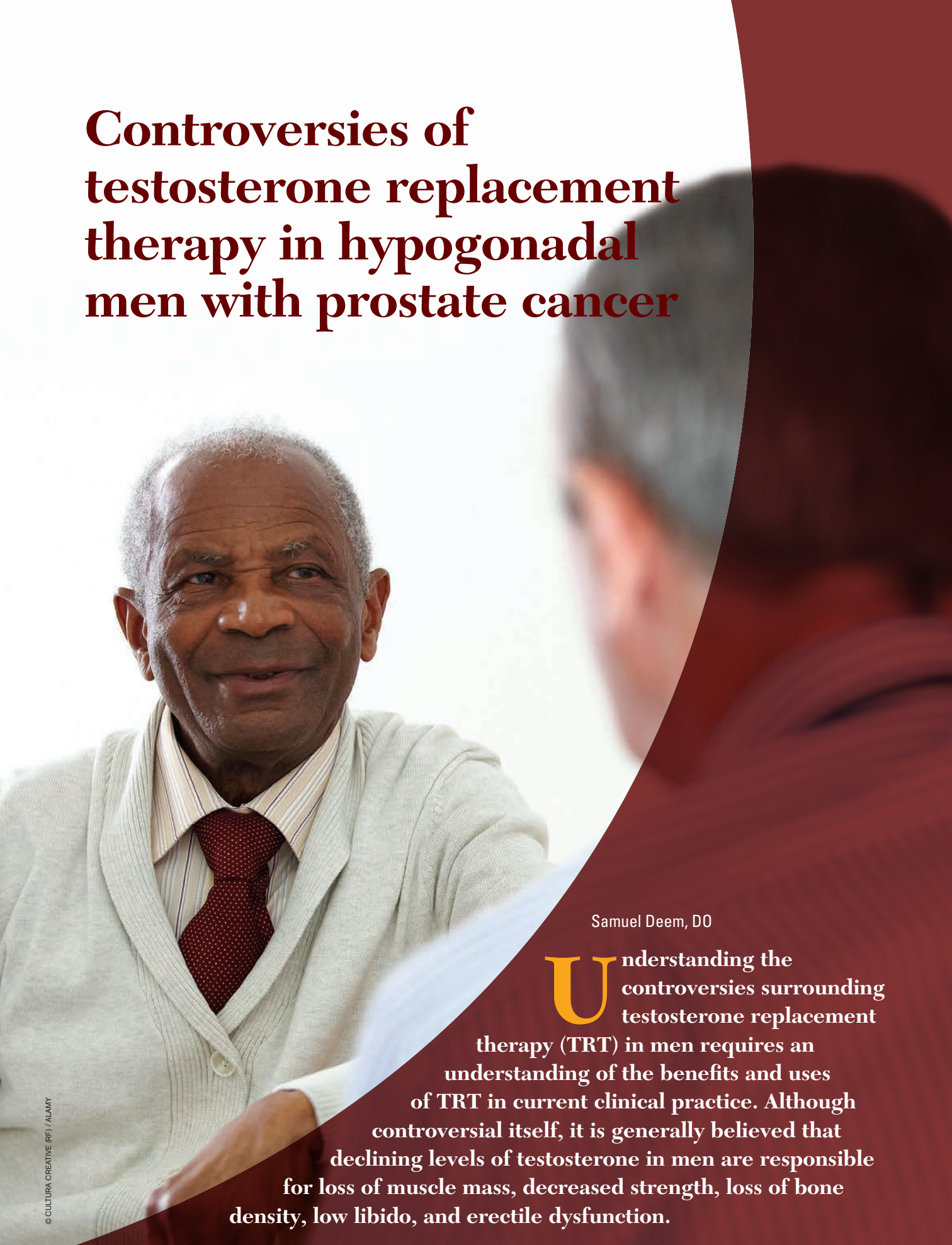
Controversies of testosterone replacement therapy in hypogonadal men with prostate cancer



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Understanding the controversies surrounding testosterone replacement therapy (TRT) in men requires an understanding of the benefits and uses of TRT in current clinical practice. Although controversial itself, it is generally believed that declining levels of testosterone in men are responsible for loss of muscle mass, decreased strength, loss of bone density, low libido, and erectile dysfunction.

Replacing testosterone using various products, including gels, patches, injections, and sublingual methods, is common and considered safe in most circumstances. However, evidence-based proof of objective benefits resulting from TRT has not been definitively shown. As a result, some suggest this practice should be considered experimental until more rigorous studies have been completed.[1] Regardless, TRT is still a very common and accepted practice in health care, which has led to multiple controversies that are currently being investigated.

One such controversy currently receiving significant media attention is the use of TRT in men diagnosed with prostate cancer. These patients include those with untreated prostate cancer, those whose prostate cancer has been treated surgically, and those treated with radiation. Prostate cancer patients being treated with androgen deprivation therapy for either metastatic or known aggressive disease are not addressed in this article, because it is universally accepted that these patients are not candidates for TRT. After categorizing these groups, the potential health benefits of TRT, including improvements in energy, vitality, sexual desire, erectile function, body composition, and bone mineral density, must be accepted as valid in order to justify the use of TRT. Based upon the precedent that TRT is beneficial in hypogonadal men, this article clarifies the controversy associated with TRT in each patient group with prostate cancer.

Though traditionally considered a contraindication to testosterone therapy, some studies have suggested that TRT use in patients with untreated prostate cancer poses little, if any, risk of progression.

Active surveillance

The value of TRT is most debatable among patients with untreated prostate cancer. Traditionally, this condition was considered a contraindication to use of TRT, which may explain why very few clinicians offer TRT in this cohort despite the lack of evidence that it is harmful. It was believed that because androgen deprivation causes prostate cancer regression, as reflected by a drop in serum prostate-specific antigen (PSA), an increase in testosterone levels might be associated with cancer progression. However, more recent findings indicate virtually no change in prostate tissue

growth, when observing men after cessation of androgen deprivation therapy, because serum testosterone levels increase above castrate range.

Maximal androgen-stimulated prostate cancer growth is seemingly achieved at relatively low serum testosterone concentrations. This has led to a belief that physiologic testosterone levels, either natural or by synthetic replacement, have no effect on growth of the prostate or prostate cancer. Although, to my knowledge, no randomized, controlled trials have been performed in this cohort, some experts believe that TRT poses minimal-to-no risk of progression in such patients based on the evidence available.

To date, there are only 2 published studies describing the use of TRT in men with untreated prostate cancer. Both of the studies are case series with a combined total of 20 patients. The first study describes observational data on 13

Table 1. PSA outcomes during follow-up for patients treated with radical prostatectomy: treatment group (TRT) versus reference group (no TRT)[5]

	ALL PATIENTS		HIGH-RISK PATIENTS		NON-HIGH-RISK PATIENTS		TRT VERSUS REFERENCE	
							P VALUE	*P* VALUE*
TREATMENT GROUP								
No. of patients	103	-	26	-	77	-	-	-
Median ng/mL/yr PSAV (IQR), No.	0.002	(0.001-0.003), 89	0.002	(0.001-0.011), 22	0.001	(0.001-0.002), 67	1.000	-
No. of suspected BCRs (%)†	4	(4)	4	(15)	0	(0)	0.015	0.03
No. of BCRs defined as a single PSA greater than 0.2 ng/mL (%)	2	(2)	2	(8)	0	(0)	-	-
No. of discontinued TRT for reason other than suspected BCR (%)‡	15	(15)	2	(8)	13	(17)	-	-
REFERENCE GROUP								
No. of patients	50	-	15	-	35	-	-	-
Median ng/mL/yr PSAV (95% CI), No.	0.0002	(-0.001-0.01), 27	0.018	(-0.012-0.106), 10	-0.0003	(-0.001-0.004), 17	-	-
No. of suspected BCRs (%)†	8	(16)	8	(53)	0	(0)	-	-
No. of BCR defined as a single PSA greater than 0.2 ng/mL (%)	5	(10)	5	(33)	0	(0)	-	-

PSA velocity (PSAV) only calculated for patients with 3 or more PSA levels in 1 or more years.

*Suspected recurrence with exclusion of patients with T3a/3b disease.

†Suspected BCR recorded when charted in medical record, if patient was referred to radiation oncologist for increasing PSA level and/or if patient underwent salvage therapy for increasing PSA.

‡Included concern for PSA, cardiovascular side effects, increased risk of relapse, cost, no symptomatic improvement, underwent operation or procedure unrelated to pancreatic cancer (CaP), supraphysiological T level, transient ischemic attack, or leg pain.

TRT, testosterone replacement therapy; PSA, prostate-specific antigen; IQR, interquartile range; BCR, biochemical recurrence; CI, confidence interval.

Source: Pastuszak AW, Pearlman AM, Lai WS, et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *J Urol.* 2013;190(2):639-644. Reprinted with permission from American Urological Association Education and Research, Inc.

patients with symptomatic hypogonadism and concomitant prostate cancer who elected active surveillance, yet received TRT. The median duration of TRT was 2.5 years, during which time no change in PSA, prostate volume, local cancer progression, or distant metastasis were observed.[2] However, in the second study, the results were less clear. Though none of the 7 hypogonadal men who underwent TRT with untreated prostate cancer developed metastatic disease, there was a detectable increase in PSA levels among 4 of the 7 patients. Of note, once the TRT was stopped, all 4 patients' PSA levels declined to their previous values.[3] Therefore, the present data are not sufficient to recommend TRT routinely for symptomatic hypogonadism in the face of untreated prostate cancer.

Radical prostatectomy

A simpler group to manage is hypogonadal men whose prostate cancer has been treated through surgical excision of the prostate. A meta-analysis of 6 articles, totaling 179 patients, explored the use of TRT in men after radical prostatectomy and revealed no biochemical recurrence, with follow-up ranging from 2.5 months to 8.5 years.[4] It is important to note that all patients included in this analysis had T1-T2 disease, a Gleason score of ≤7, serum PSA level of ≤10 ng/mL, negative surgical margins, and no lymph node (LN) involvement. In those patients with low risk of recurrence with no measurable serum PSA and no adverse features, such as positive surgical margin, seminal vesicle involvement, or Gleason score of ≥8, it appears relatively safe to treat with TRT.

Encouraging data are emerging regarding the use of TRT in hypogonadal men treated with radiation therapy for prostate cancer.

A recent retrospective analysis of 103 patients who underwent radical prostatectomy and then subsequently received TRT was performed. Twenty-three of the 103 patients had adverse features, including a Gleason score of ≥8, positive surgical margins, or LN involvement. Despite the presence of high-risk features, after 36 months of follow-up this analysis revealed twice as many biochemical recurrences, defined as consecutive increases in PSA levels, in the control group than in the TRT group.[5] This study

Table 2. Most recent prostate-specific antigen level in 31 men on testosterone-replacement therapy from 1.5 to 9.0 years after brachytherapy

PSA, ng/mL	No. of Patients (%)
<0.1	23 (74.2)
<0.5	30 (96.7)
<1.0	31 (100)

PSA, prostate-specific antigen

Source: Morales A, Black AM, Emerson LE. Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. *BJU Int.* 2009;103(1):62-64. Reprinted with permission; © 2006 American Cancer Society.

is significant in the sense that even patients at high risk of prostate cancer recurrence can cautiously be given TRT, when needed. Hypogonadal men with localized prostate cancer treated with radical prostatectomy may be considered for TRT after a prudent interval, if there is no clinical or laboratory evidence of residual cancer.

Radiation therapy

Despite current literature supporting the use of TRT after radical prostatectomy, the use of TRT after radiation therapy presents a potential concern. At issue is the known and expected fluctuation of serum PSA levels subsequent to radiation therapy for prostate cancer.

Because PSA is relied on as the primary oncological marker of prostate cancer in patients receiving TRT, the unpredictability of the PSA after radiation therapy presents a challenge in interpreting the effects of TRT. Currently, there are 4 studies published, totaling 55 patients, that have examined the use of TRT after radiation therapy for treatment of prostate cancer. Analysis of these studies revealed that 23 patients were treated with brachytherapy, 21 with external beam radiotherapy, and 11 with both. The average follow-up period ranged from 12 months to 4.5 years. None of the studies detected prostate cancer recurrence or progression, despite increased PSA values.[6-9] It is important to note that biochemical recurrence (BCR) in the setting of radiation therapy is defined according to the Phoenix criteria as PSA nadir + 2 ng/mL. This definition allows for PSA levels to rise somewhat before being defined as BCR. Although the data are encouraging, the use of TRT in the setting of prostate cancer treated with radiation therapy is still in its infancy.

Final notes

Although controversy over the use of TRT in the setting of prostate cancer still exists, the data derived from the current literature would suggest that TRT may be used safely. Hypogonadal men with prostate cancer must clearly understand the risks and benefits of TRT and be compliant with vigilant follow-up. Most experts suggest obtaining written consent before implementation of TRT. In addition, the physician must exercise caution because the safety data remain limited.

In February 2014, the American Urologic Association Position Statement on Testosterone Therapy stated that the current evidence does not provide any definitive answers regarding the risk of TRT on prostate cancer.[10] Further research with prospective data and longer follow-up are necessary in order to end the controversy of TRT in the hypogonadal man with prostate cancer.

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