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Male Endocrinology

Can testosterone therapy be offered to men on active surveillance for prostate cancer? Preliminary results

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This report presents our experience with T therapy in a cohort of T-deficient men on active surveillance (AS) for Gleason 3 + 3 and Gleason 3 + 4 prostate cancer (PCa). A retrospective chart review identified 28 men with T deficiency who underwent T therapy (T group) for at least 6 months while on AS for PCa. A comparison group of 96 men on AS for PCa with untreated T deficiency (no-T group) was identified at the same institution. The AS protocol followed a modified Epstein criteria and allowed inclusion of men with a single core of low-volume Gleason 3 + 4 PCa. Mean age was 59.5 and 61.3 years, and mean follow-up was 38.9 and 42.4 months for the T and no-T groups, respectively. Of all 28 men in the T group, 3 (10.7%) men developed an increase in Gleason score while on AS. Of 22 men in the T group with Gleason 3 + 3 disease, 7 (31.8%) men developed biopsy progression including 3 men (13.6%) who developed Gleason 3 + 4 PCa. Of 6 men with Gleason 3 + 4 disease at baseline, 2 (33.3%) men developed an increase in tumor volume, and none developed upgrading beyond Gleason 3 + 4. All 96 men in the no-T group had Gleason 3 + 3 disease at baseline and, 43 (44.7%) developed biopsy progression, including 9 men (9.38%) with upgrading to Gleason 7 (3 + 4). 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.

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INTRODUCTION

The "androgen hypothesis" that testosterone (T) accelerates prostate cancer (PCa) has been taught to generations of physicians since the seminal work by Huggins and Hodges in 1941.[1] For this reason, any history of PCa has been considered an absolute contraindication to T therapy. However, a number of case series have now reported reassuring results with T therapy in men after radical prostatectomy,[2] brachytherapy,[3,4] and external beam radiation.[5] These results are consistent with a shift in our understanding of the relationship between androgens and PCa. There is now considerable scientific evidence that supports a saturation model in which PCa is highly sensitive to changes in androgen levels at very low concentrations, but reaches a saturation point at relatively low concentrations, beyond which further increases in androgen concentrations have little or no effect.[6]

The ultimate test of this model is T therapy for men who are on active surveillance (AS) for untreated PCa. Instead of undergoing treatment for low-risk prostate cancer, men on AS are monitored for signs of more aggressive disease. While there is no standard AS protocol, most published protocols monitor patients with PSA levels and digital rectal exams (DRE) several times a year and with repeat prostate biopsies at 1–2 years intervals.[7–9] While definitions for biopsy progression vary, overall between 12% and 30% of men on AS will progress from AS to treatment over the short-term.[10]

Men on AS may develop symptoms of T deficiency and seek care for this condition. However, published experience with T therapy in these men has been limited to case reports[11] and one series of 13 men with Gleason 3 + 3 cancer.[12] In that series, none of 13 men developed definite biopsy progression after a mean of 2.5 years of T therapy. In a separate small series, there was an increase in PSA for a few men with PCa who were treated with T.[13] Leibowitz *et al*. reported mixed results with T therapy in a heterogenous population of men with PCa, including men with advanced disease.[14]

We present our single-center experience with T therapy in a larger group of men on AS for PCa, including for the first time a group of men with more aggressive Gleason 3 + 4 disease. We compare rates of biopsy progression with a cohort of men also undergoing AS with untreated low serum T concentrations in a different practice within the same institution. Based on the literature and current concepts regarding androgens and PCa, we wished to test the hypothesis that T therapy would not increase rates of biopsy progression beyond rates observed in men who did not undergo T therapy.

MATERIALS AND METHODS

We report the experience with T therapy in T-deficient men undergoing AS at Men's Health Boston (MHB), an outpatient men's health center affiliated with Beth Israel Deaconess Medical

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Center (BIDMC). We compare rates of biopsy progression with a separate cohort of men treated by a separate physician (WCD) at BIDMC. Retrospective chart reviews for each cohort were approved by the BIDMC Institutional Review Board. A total of 28 men were identified who underwent T therapy at MHB for T deficiency while on AS for a minimum of 6 months (T group). Clinical manifestations in all men were severe enough so that patients were willing to accept treatment despite the known concerns of treatment in men with PCa. A total of 96 men on AS for PCa were identified at BIDMC with biochemical T deficiency, none of whom received T therapy (no-T group). This cohort represents a subset of a larger population of men on AS for which results have been previously reported.[15] Baseline clinical and hormonal characteristics were determined, as well as prostate biopsy results.

Selection criteria

Biochemical T deficiency was defined as a total T of <350 ng dl^{-1} or a free T of <1.5 ng dl^{-1} as measured by radioimmunoassay, or calculated free T of <100 pg ml^{-1}.[16] All men treated with T had presenting symptoms of erectile dysfunction, diminished libido, and/or fatigue. All patients had to demonstrate sufficient understanding of the lack of safety data, and willingness to sign an informed consent form. The inclusion criterion for AS was based on pathology on biopsy only. Men with Gleason 6 PCa in <3 cores, with no more than 50% of any core involved by the tumor were included in the analysis. We additionally included men on AS with a single core of Gleason 7 (3 + 4) on biopsy.

Active surveillance protocol

All men underwent PSA and DRE approximately every 3–6 months. Prostate biopsy was performed every 12–18 months, or more frequently if indicated based on PSA rise or change on DRE. Men in the T therapy cohort underwent 12-core biopsy, whereas men in the comparison cohort underwent 20-core biopsy. Most of the pathologic specimens were sent for evaluation by the same pathology team at the same institution. The remaining samples were evaluated at an academic tertiary medical center in the same city. Biopsy progression was defined as either an increase in Gleason score or an increase in tumor volume. The increase in tumor volume was defined as 3 or more positive cores, or more than 50% involvement in a single core. Men with biopsy progression were offered definitive treatment.

Statistical methods

Rates of upgrading and biopsy progression were compared between groups using Fisher's exact test. Changes in serum PSA and T levels were compared using Student's *t*-test as appropriate. Bonferroni's correction was used for all three-way comparisons.

RESULTS

Baseline characteristics and rate of pathologic upgrading for the T therapy and comparison cohorts are listed in **Table 1**. Mean ages were 59.5 years for the T group and 61.3 years for the no-T group, with a mean follow-up of 38.9 and 42.4 months, respectively. For the treatment cohort, Gleason scores at baseline were 6 in 22 men and 7 (3 + 4) in 6 men. All men in the no-T group had Gleason 3 + 3 at baseline. There was no difference in mean baseline total or free T between the T and no-T group ($P = 0.120$ and $P = 0.911$) or between men with Gleason score 6 and men with Gleason score 7 ($P = 0.881$ and $P = 0.709$). All men treated with T reported improvement in libido, erectile function, and/or energy. T therapy was initiated with T cypionate injections (14 men), topical gels (8 men), and T pellets (6 men). Mean serum T concentrations increased with treatment by 469 ng dl^{-1} ($P < 0.0001$). No man in either cohort developed metastatic disease or died from prostate cancer. One man in the T group died from accidental head trauma.

T group – Men with baseline Gleason 3 + 3 (22 men)

The mean age was 61.6 years, and mean follow-up was 42.9 months. While on T therapy and AS, mean PSA increased by 1.04 ± 2.73 ng dl^{-1}, although this increase did not reach statistical significance ($P = 0.0748$) (**Figure 1**). Three men (13.6%) had an increase in Gleason score to 3 + 4 on surveillance biopsies. One continued on AS with a subsequent biopsy showing no prostate cancer. One man elected treatment with radiation therapy, and one man elected radical prostatectomy. All three men with an increase in Gleason score remain on T therapy. An additional four men had biopsy progression due to an increase in tumor volume without any increase in Gleason score above 3 + 3. Two of these men sought definitive treatment with radiation (1) or radical prostatectomy (2). Two men continued on AS, one of whom had no cancer on a subsequent biopsy. In total, two men underwent radical prostatectomy, one who had an increase in Gleason score, and one who had an increase in tumor volume. Both of these men had Gleason 3 + 4 disease in the prostate specimen and have undetectable PSA levels at most recent follow-up.

T group – Men with baseline Gleason 3 + 4 (6 men)

The mean age for the six men was 61.2 years, and mean follow-up is 24.2 months. At baseline, five men had one core with Gleason 3 + 4 disease occupying between <5% and 25% and no other cancer in any cores. One man had one core with 5% Gleason 3 + 4 and one core with Gleason 3 + 3 disease. Four men received T therapy with T cypionate injections, one was treated with pellets, and one was treated with topical gels. While on T therapy and AS, mean PSA increased by 0.54 ± 1.02 ng dl^{-1}, which did not reach statistical significance ($P = 0.302$) (**Figure 1**). Two men did not have any cancer identified on any surveillance biopsies. No man had an increase in

Table 1: Baseline characteristics and rate of progression for 28 men on T therapy while on AS for PCa and a comparison cohort of 96 men with untreated T deficiency on AS

	T group (n=28)	*T group: Gleason 3+3 (n=22)*	*T group: Gleason 3+4 (n=6)*	*No-T group (n=96)*	*P (T group vs no-T group)*
Age (years)	59.4±8.1	61.6±8.75	61.2±10.1	61.3±6.9	0.221
Baseline total T (ng dl^{-1})	328.2±135.6	321.9±117.6	333.8±160.6	369.8±133.2	0.150
Baseline free T (ng dl^{-1})	0.89±0.7	0.95±8.01	0.82±3.62	0.88±0.34	0.917
Baseline PSA	3.29±2.50	3.21±2.63	2.58±1.64	4.46±2.98	0.061
Increase in PSA	1.02±2.65	1.04±2.73	0.54±1.02	0.22±2.87	0.183
Follow-up on AS (months)	38.9±18.6	42.9±16.5	24.2±20.2	42.7±24.0	0.442
Increase in Gleason score (%)	3 (10.7)	3 (13.6)	0	9 (9.38)	0.732
Biopsy progression (%)	9 (32.1)	7 (31.8)	2 (33.3)	43 (44.7)	0.280

Means are expressed as mean±s.d. PCa: prostate cancer; AS: active surveillance; PSA: prostate specific antigen; s.d.: standard deviation

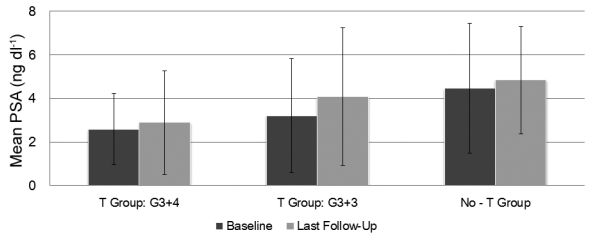

Figure 1: Mean PSA at baseline and at last follow-up for men treated with T therapy for Gleason 3 + 3 and Gleason 3 + 4, in addition to a comparison cohort of men on AS for Gleason 3 + 3 who have untreated T deficiency.

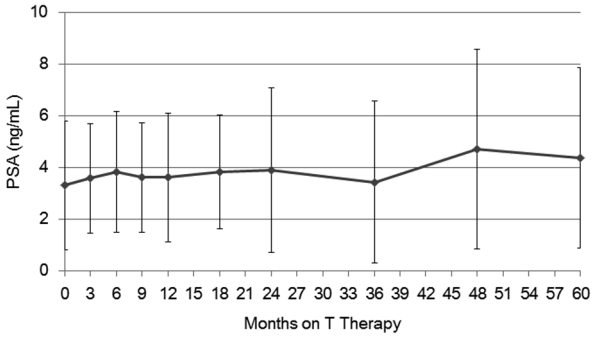

Figure 2: Mean PSA during T therapy for all 28 men on AS for PCa. Error bars represent 95% confidence intervals. Mean change in PSA for all 28 men is 1.02 ± 2.65.

Gleason score above 3 + 4 on surveillance biopsies. Two men had an increase in tumor volume without an increase in Gleason score. One of these men had an increase from one positive core on the initial biopsy to four positive cores on surveillance biopsy. He elected treatment with radical prostatectomy, and only Gleason 3 + 3 disease was found in his prostate specimen, despite the presence of Gleason 3 + 4 on his initial biopsy. An additional man plans to undergo radical prostatectomy. The remaining four men remain on AS, and all six men remain on T therapy.

No-T comparison group (96 men)

Mean age was 61.3 years and mean follow-up was 42.4 months. Mean total and free T were 369.8 ± 133.2 ng dl^{-1} and 0.88 ± 0.34 ng dl^{-1}, respectively, not statistically different from baseline values for the T groups (P = 0.539). Mean PSA increased by 0.22 ± 2.87 ng dl^{-1} while on surveillance. A total of 43 men (44.7%) developed biopsy progression including 9 men (9.4%) with upgrading from Gleason 6 to Gleason 7 (3 + 4). The remaining 34 men (35.4%) had biopsy progression based on the increase in tumor volume alone.

There was a nonsignificant increase in mean PSA increased for all three groups (**Figure 1**) and the increase in PSA for the entire T group also did not reach significance (P = 0.0739) (**Figure 2**). The percentage of men demonstrating increased Gleason score on restaging biopsy was similar for the T group and the no-T group (10.7% *vs* 9.4%, OR 1.16 [0.292–4.61 95% CI]; P = 0.732). The rate of overall biopsy progression (increase in either Gleason score or PCa volume) was lower for men on T therapy, but this difference did not reach statistical significance (32.1% *vs* 44.7%, OR 0.584 [0.240–1.42 95% CI]; P = 0.280). There was no significant difference in the negative biopsy rate for men receiving T compared to men in the no-T group (10.7% *vs* 6.25%; OR 1.92 [0.449 − 8.22 95% CI]; P = 0.421). There was no significant difference in the rate of biopsy progression among patients with baseline Gleason 3 + 3 disease who received T versus those who did not (31.8% *vs* 44.7%; P = 0.341). The rate of biopsy progression was not different within the T group for men with baseline Gleason 3 + 3 and baseline Gleason 3 + 4 disease (31.8% *vs* 33.3%; P = 1.00).

DISCUSSION

In this study, we present the largest series to date of men on AS treated with T therapy. For comparison, we additionally describe a cohort of men with untreated T deficiency followed on AS for PCa. Due to differences between the two groups in the AS selection criteria and surveillance protocols, the untreated group must be regarded as a comparison group rather than a true control group. Direct statistical comparison between these two groups should not be interpreted as a true comparison of oncologic risk between T treated and control groups.

Important differences between these two cohorts include: (1) inclusion of men with low-volume Gleason 7 (3 + 4) disease in the T-treated group whereas the no-T cohort was comprised only of men with Gleason 6 disease; and (2) a more aggressive biopsy protocol for the no-T cohort, with 20-core biopsies compared with 12-core biopsies in the T group. Key features of the no-T group that support its use for comparison purposes include populations from the same geographical catchment area, and importantly, selection of men meeting similar biochemical criteria for T deficiency.

Among men on AS, who received T therapy, there was no significant increase in serum PSA, and the overall rate of biopsy progression among men on AS who received T therapy was 32.1%, with most instances of progression based on increased volume of disease, and only 10.7% due to increased Gleason score. None of the men with Gleason 7 disease demonstrated increased Gleason scores on subsequent biopsy.

These results were similar to biopsy progression rates observed in the no-T comparison group, for which overall progression was noted in 44.7% and increased Gleason score in 9.4%. Biopsy progression rates for men who received T therapy also fall well within published rates in other contemporary series of men with multiple repeat biopsies on AS[7–10] (**Table 2**).

This is the first report on T therapy for a group of men on AS for documented Gleason 3 + 4 PCa. Although the number of patients with Gleason 3 + 4 PCa is very small and the follow-up is shorter than for men with Gleason 3 + 3, the inclusion of these men is important because approximately one-third of men with presumed Gleason 3 + 3 PCa actually harbor occult Gleason 3 + 4 or higher disease.[17] Among these six men, the rate of biopsy progression was not higher than for men treated with T with Gleason 3 + 3 disease, or in comparison to historical controls, some of which include selected men with Gleason 3 + 4 disease.

The relationship between T and PCa is of considerable importance today, as there are now large numbers of men diagnosed or treated with PCa and widespread recognition of the clinical impact of T deficiency. A number of studies have reported benign outcomes with T therapy after various forms of treatment for PCa, including radical prostatectomy, brachytherapy, or radiation therapy,[2,5] In comparison, there are currently few published reports on outcomes with T therapy for men with untreated PCa.[12] The data presented here indicate that T therapy may not increase the oncologic aggressiveness of low to intermediate risk prostate cancer over the short- to medium-term. Definitive clinical trials will be required to assess the safety of T therapy in men on AS.

There are several limitations to this study including the retrospective nature of the study and differences in the AS protocols.

Table 2: Biopsy progression in the T and no-T groups, along with historical controls

Cohort	*n*	*AS eligibility*	*Number of biopsy cores*	*Follow-up (months)*	*Definition of biopsy progression*	*Any biopsy progression (%)*	*Progression by increase in Gleason score (%)*
T group Current study	28	Gleason 3+3, <3 core involved, <50% in any core *Included: 6 men with low-volume Gleason 3+4*	12	39	Increase in Gleason score *or* 3+ positive cores *or* >50% of a single core	32.1	10.7
No-T group Current study	96	Gleason 3+3, <3 cores involved, <50% in any core	20	42	Increase in Gleason score *or* 3+ positive cores *or* >50% of a single core	44.7	9.4
Cary *et al*.[7]	465	Clinical stage T1–T2, PSA <10 ng dl^{-1}; Gleason 3+3, <33% positive cores, <50% in any core *Included: 31 men with low-volume Gleason 3+4*	10 or more	51	Any increase in primary or total Gleason score *or* an increase in volume >33% positive cores *or* >50% of a single core	47.3	11.8
Tosoian *et al*.[8]	769	Clinical stage T1c, PSA density <0.15 ng dl^{-1}, Gleason 3+3, <3 cores involved, <50% in any core	12–14	32	Increase in Gleason score *or* 3+ positive cores *or* >50% of a single core	30.6	13.8
Adamy *et al*.[9]	238	Clinical stage T1–T2a, PSA 10 ng dl^{-1}, Gleason 3+3 or less, <3 cores involved, <50% in any core	10 or more	22	Increase in Gleason score *or* 3+ positive cores *or* >50% of a single core *or* increase in stage over T2a	21.7	15.2

AS: active surveillance; PSA: prostate specific antigen

Men in the comparison cohort were monitored with 20-core biopsies whereas men in the treatment cohort were monitored with 12-core biopsies. This difference may have driven the observed higher rate of increase in tumor volume in the comparison cohort, although an increase in cores above 12 has been shown to lead to only marginal increases in diagnostic yield.[18] Prostate volumes were not reliably available from the medical record, and it is not clear how prostate volume may have affected the results. All men in this study had low-volume disease, and the results described here cannot be assumed to pertain to men with larger-volume or higher-risk disease.

Given the small number of men in this study that received T therapy while undergoing AS, these data must be regarded as preliminary and these results should not influence treatment decisions regarding the use of T in men on AS. However, these results have potentially important clinical implications. Men may develop symptomatic T deficiency while on AS, and men who are already on T therapy may be diagnosed with low-risk PCa and be candidates for AS.

Historically, T therapy was contraindicated in these men due to the belief that such treatment would cause rapid PCa growth or more aggressive disease, even though systematic reviews of the literature have not supported this view.[19,20] Although there is minimal published experience with T therapy in men on AS, and such treatment may seem risky based on traditional beliefs regarding the biological relationship of T and PCa, it should be considered that approximately one in seven T-deficient men with PSA <4.0 ng ml^{-1} will have PCa identified if those men were subjected to biopsy,[21,22] meaning that clinicians already provide T therapy to substantial numbers of men with untreated, albeit clinically undiagnosed, PCa. Treatment of these men has not been shown to increase PCa rates.[23,24]

The preliminary data presented here suggest that T administration does not cause short-term biopsy progression or rapid PCa growth in men undergoing AS, contradicting the long-held belief that higher androgen concentrations necessarily cause rapid PCa growth. For men with T deficiency, T therapy can lead to improvement in energy, libido, and sexual function and may also improve metabolic function, bone density, and overall quality of life.[25] Given the large numbers of men who are candidates for AS, and who may also be symptomatic from T deficiency, there is a need for prospective controlled studies of T therapy in these men to assess safety and benefits.

We here present the largest series to date of men treated with T while on AS for PCa. The rate of biopsy progression was not greater than observed in a comparison cohort of men on AS with untreated T deficiency, or historical controls. In the absence of obvious harms, we continue to offer T therapy to selected men on AS for PCa. In our practice, we did not routinely discontinue T therapy for a rising PSA alone. In cases where progression was noted by follow-up biopsy, we usually recommended discontinuation of T therapy, with the possibility of resuming T therapy after the prostate cancer had been treated.

AUTHOR CONTRIBUTIONS

RK, AM, WCD, and IFS conceived of the study, participated in study design and contributed revisions to the manuscript. RK performed the statistical analysis and drafted the manuscript. MH participated in data collection and revision of the manuscript. PAR and WPC participated in data collection and analysis. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

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