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Testosterone Therapy In Patients With Treated and Untreated Prostate Cancer: Impact on Oncologic Outcomes

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Abstract

Purpose—Both testosterone deficiency (TD) and prostate cancer (CaP) have increasing prevalence with age. However, because of the relationship between CaP and androgen receptor activation, testosterone therapy (TT) among patients with known CaP has been approached with caution.

Materials and Methods—We identified a cohort of 82 hypogonadal men with CaP who were treated with TT. These included 50 men treated with Radiation Therapy (XRT), 22 with Radical Prostatectomy (RP), 8 managed with Active Surveillance (AS), 1 with Cryotherapy and 1 with High-Intensity Focused Ultrasound. We monitored prostate specific antigen (PSA), testosterone, hemoglobin, biochemical recurrence (BCR) and PSA Velocity (PSAV).

Results—Median patient age was 75.5 years and median follow up was 41 months. We found an increase in both testosterone ($p < 0.001$) and PSA ($p = 0.001$) levels in the entire cohort. PSA increased in the AS patients, however no patients were upgraded to higher Gleason Score on subsequent biopsies, and none have yet gone on to definitive treatment. We did not have any cases of BCR amongst RP patients, but 3 XRT patients (6%) experienced BCR. It is unclear whether these were related to TT or reflected the natural biology of their disease. We calculated the mean PSAV to be 0.001, 0.12, and 1.1 ug/L/yr for the RP, XRT, and AS groups, respectively.

Conclusions—In the absence of randomized placebo controlled trials, our study supports the hypothesis that TT may be oncologically safe in hypogonadal men following definitive treatment or active surveillance for CaP.

Keywords

testosterone therapy; testosterone deficiency; androgen replacement; prostate cancer; biochemical recurrence

Introduction

The prevalence of testosterone deficiency (TD), (previously known as late-onset hypogonadism) is between 3.1 to 7% in men less than 70 years of age, and 18.4% in those greater than 70 years¹. It is characterized by low serum testosterone indices and a constellation of symptoms and physical changes incrementally related to the degree of deficiency. Several published series confirm the ability of exogenous T therapy (TT) to replenish serum levels of testosterone with an improvement in symptoms². Despite this knowledge, the use of TT was restricted based on research by Huggins in the 1940's³ indicating that CaP growth was linearly related to testosterone concentration.

Over the past two decades, evidence has accumulated in opposition to these long held views, bringing TT into the forefront of men's health. In a 2004 New England Journal of Medicine review article, Rhoden et al found no increased risk of CaP in men treated with TT⁴. In 2006, Morgentaler examined Huggins' research and discovered that there was no scientific evidence to suggest that TT leads to CaP growth⁵. With a growing body of evidence to suggest the safety of TT, a new theory, "the saturation model," was developed. This model provided an answer to the paradox of why castration effectively reduced PSA, while raising T may not worsen CaP or increase PSA. In hypogonadal men, it also helped explain why an initial increase in PSA did not necessarily reflect disease progression. The saturation model suggests that T exerts its maximal effect on androgen receptors and CaP growth at very low concentrations while having little to no impact at higher concentrations⁶. This new model provides a foundation for TT in men with, or at risk for, CaP.

In this retrospective review, we describe our experience of TT in a cohort of patients with either actively treated CaP or those on AS for low risk cancer.

Materials and Methods

We searched the electronic medical records at the Vancouver Prostate Center at Vancouver General Hospital and the Victoria General Hospital for the keywords: "testosterone replacement; testosterone deficiency; androgen" among active prostate cancer patients from September 2011 to March 2015. For each patient we documented his prostate cancer pathology, d'Amico risk score,⁷ testosterone values, type and duration of TT, sequential PSA values, incidence of BCR, and overall clinical course. We performed statistical analysis using paired, two-tailed t-tests. Amongst surgical patients, we defined BCR by AUA guidelines: a postop PSA >0.2ug/L with a second confirmatory PSA of over 0.2ug/L⁸. We defined BCR amongst patients receiving radiation therapy using the PHOENIX criteria: a 2ug/L rise over post treatment PSA nadir⁹. We calculated PSAV in patients who had at least 3 PSA measurements. This unfunded study received approval from the UBC Clinical Research Ethics Board.

Results

We identified 166 patients from the EMR under the combined search terms of "testosterone" and "prostate cancer". We excluded 42 who did not receive TT, 30 patients who received TT prior to their CaP diagnosis, 1 patient who did not have prostate cancer, and 9 patients with

incomplete data. Only patients with TT for at least 3 months were included. Information from follow-up clinic notes were used to document compliance on TT. All men treated with T had presenting symptoms of one or more of: erectile dysfunction, fatigue, reduced libido, mood changes and weakness. The remaining 82 patients with a diagnosis of CaP and on TT are the basis of this report.

Among these patients, 22 were treated with RP, 37 with external beam radiation therapy (EBRT), 13 with brachytherapy, 1 with HIFU, and 1 patient with cryotherapy. We followed 8 men who were managed by AS. Frequencies of Gleason 6, 7, 8, and 9 disease was 32/82, 39/82, 7/82 and 4/82 men, respectively. 21 men in our cohort received neoadjuvant ADT; 6 in the RP group and 14 in the XRT group, with the cryotherapy patient also receiving neoadjuvant ADT. Table 1 summarizes the testosterone and PSA characteristics of each of these groups.

The median age of the study group was 75.5 years (IQR 70-82 years) at the time of last follow up. The median follow up after initiating TT was 41 months (IQR 22-57 months). While on TT the median hgb level measured was 149 g/L, (IQR 140-157 g/L) and this was significantly higher than the median Hgb prior to TT (143 g/L, IQR 131-149 g/L, $p = 0.046$). The median pre-TT testosterone (6.3 mmol/L, IQR 4.55-7.7 mmol/L) increased significantly after TT initiation (13.2 mmol/L, IQR 7.7-20.8 mmol/L, $p < 0.001$). This difference in testosterone remained statistically significant in all risk groups and all treatment groups (Figure 1).

For the entire cohort, as well as for treatment and risk groups, PSA values prior to TT initiation were compared to PSA values at the last follow-up time (median 41 months) following TT (figure 2). Overall, PSA was significantly increased after TT ($p = 0.001$). Subgroup-analysis of the RP, XRT, and AS patients showed a significant increase in PSA in each group ($p = 0.048$, $p = 0.028$, $p = 0.003$, respectively) (figure 3,4,5). When analyzed by d'Amico risk groups, only low risk CaP patients had a significant increase in their PSA after TT ($p = 0.006$). However, with the removal of AS patients from the overall low-risk group, there is no significant difference in PSA increase after TT ($p = 0.37$). Post-TT PSA values did not differ by route of testosterone delivery: transdermal (N=54), intramuscular (N=8), oral (N=5) or mixed (a combination of 2 or more modalities; N=15).

We analyzed BCR and PSAV in all groups. Amongst the 22 RP patients, there were no incidences of BCR. Of the 50 in the XRT group, there were 3 patients who experienced BCR (6%), all after EBRT. Two of these men were high-risk patients and one was intermediate risk. BCR occurred on average at 10.7 months (range, 3-18 months) after initiation of TT. In all 3 cases TT was stopped after BCR was identified and they have been followed for an average of 40 months after BCR. Following cessation of TT, one of these three patients, who had high-risk, Gleason 4+3 disease, with initial T of 8.8 nmol/L received ADT and has developed pelvic metastases, while the other two (both with Gleason 3+4 and initial T of 0.68 and 3.5 nmol/L) have not received ADT or experienced further disease progression, with one deciding to remain on TT to control symptoms of T deficiency. In all 3 cases of BCR, PSA remained elevated (mean PSA = 5.13 ng/ml) upon withdrawal of TT compared to

baseline PSA levels (mean PSA = 1.40 ng/ml, $p=0.02$). None of these patients had received neoadjuvant ADT.

Median PSAV was undetectable in all RP patients, 0.018 ng/ml/yr in the XRT group and 0.48 ng/ml/yr in AS patients. Amongst risk groups, the median PSAV was 0.02 in high risk, undetectable in medium risk, and 0.05 ng/mL/year in low risk patients (Figure 2).

All AS patients ($n=8$), had low volume Gleason 6 cancer and were followed for a median of 27 months (IQR 15-46 months). None have shown clinical or pathologic progression and none have gone on to definitive treatment. Two of the AS patients were diagnosed on Transurethral resection of the prostate (TURP) and did not have subsequent confirmatory biopsies. The remaining 6 patients have had an average of 3 post-diagnosis biopsies. In these 6 low risk patients, only one follow-up biopsy revealed persistent Gleason 6 disease and the 5 others had no evidence of disease. Overall, 2 AS patients were taken off TT due to early PSA increases; however, upon withdrawal of TT each PSA value returned to a value (mean PSA = 4.23 ng/ml) similar to their pre-TT level (mean PSA = 4.41 ng/ml, $p=0.3$).

Discussion

In the current study, we reviewed patients with localized CaP treated with curative intent and patients with active CaP on AS. In all treatment scenarios, we demonstrated an increasing trend in PSA over the course of TT. When analyzed by risk group, only low-risk CaP patients had a significant increase in PSA. This was found to be entirely attributable to the AS patients in that group. When removed, no risk group showed a significant increase in PSA. We hypothesize that this is due to the AS patients having both untreated prostate cancer and healthy prostate tissue insitu, and thus, has the capacity to respond to TT with an increase in PSA in comparison to men with removed or radiated prostates. A prospective, randomized trial on TT in AS patients would be able to confirm this hypothesis.

Amongst the RP patients, PSA increased with no signs of BCR after a median of 48 months of follow up. These results are consistent with other reports that support the use of TT in hypogonadal men with fully treated CaP¹⁰⁻¹³. The lack of BCR in our series, compared to the BCR rate of 31.4% in a large retrospective review of 4561 men¹⁴ may support Pastuszak et. al.'s observation that BCR was lower amongst those receiving TT compared to a control group¹⁵.

Patients on AS have low risk, but active prostate cancer cells in situ. Of our 8 subjects followed on AS, no patients were upgraded on subsequent biopsies or clinical evaluation. The largest study to date of AS patients supports our findings. Kacker et al retrospectively compared 28 men on AS with TT to 96 men on AS without TT. They found no difference in rates of biopsy progression over 3 years¹⁶.

Patients receiving HIFU & cryotherapy both had trending increases in PSA with respective PSAV's of 0.31 (low risk) and 0.8 (high risk). This may represent BCR in these individuals.

In our 50 XRT patients, there were 3 cases of BCR over a median of 40 months follow up. Several possibilities exist to explain our cases of BCR. The largest trial tracking rates of

BCR amongst XRT patients documented a rate of 22.6% amongst 2694 patients undergoing EBRT at a median occurrence of 57 months¹⁷. Given that our series documents a BCR rate at 3/50 (6%) amongst RT patients, it is unclear whether this represents baseline recurrence, BCR due to TT, or a decreased rate of BCR with TT.

The saturation model⁶ adds an alternative explanation for our 3 cases of BCR, in addition to explaining why all subjects in our trial developed a small but significant rise in PSA after TT was initiated. The prostatic androgen receptors become saturated with a serum T concentration of around 240-250 ng/dl (8-8.7 nmol/L)¹⁸. Below this saturation point, PSA is seen to increase in a linear fashion with increasing testosterone, but the relationship becomes uncoupled after this point¹⁹. The amount of PSA increase in these hypogonadal men is on average 0.3 ng/dL²⁰. In our trial, two men with BCR but no other signs of clinical progression both had T below the saturation point, while one patient with a T above the saturation point developed radiologic and clinical progression of his disease. This may suggest that these first two cases of BCR instead represent a normal PSA response to treatment of hypogonadal T. Despite these possibilities, there is a naturally occurring BCR rate without TT, and individual cases cannot form the basis of a causative statement on BCR rates.

Finally, we analyzed PSA increase based on testosterone administration method. A recent meta-analysis analyzed the effect of TT modalities and found an increase in PSA, but no short-term CaP risk regardless of administration method²¹. Our series replicated these results, in that all four categories (IM, PO, Transdermal, Mixed) showed a significant increase in PSA after TT.

At present, several clinical trials involving TT are in progress. Of closest relevance to this paper is a study aiming to assess TT among patients with non-metastatic castrate resistant CaP (NCT01187485²²). However, at present no trials are addressing the use of TT following treatment for localized CaP or during AS.

In light of this, the best evidence that has been generated is overwhelmingly in favour of the safety of TT amongst patients with treated and untreated CaP²³. The saturation hypothesis is supported by basic science research going back to 1968²⁴. A 2015 review summarizes over a dozen studies in support of TT¹⁸. This paper includes men with RP, XRT, and AS who have all received TT without worse outcomes. TT prior to a diagnosis of CaP has gained evidence of safety as well. Retrospective population-based studies have found no association between TT and high-grade CaP,²⁵ and no association between TT and overall survival, cancer-specific survival, or aggressive prostate cancer²⁶.

The saturation model helps explain these findings, and explains why all treatment groups displayed an increase in PSA. The median T prior to TT across all subjects was below the saturation point at 6.3 nmol/L. This would place any remaining prostate tissue below the saturation zone, and thus able to respond to T with a rise in PSA. As the model predicts: only for a narrow, low range of T will prostatic androgen receptors respond, after which point they become saturated and unable to respond further to additional T. Thus we would expect to see an initial, small rise in PSA, with no worsening of cancer growth after the

saturation point has been reached. This is reflected in our results, and in the results of many others.

In light of the preliminary evidence of safety with TT in CaP, findings are emerging which may suggest an overall benefit to CaP outcomes with TT in hypogonadal men. In our trial, we display a rate of BCR in RP and XRT patients far below the natural recurrence rate of 15-40% reported in the literature¹⁷, a finding seen in other, similar studies¹⁵. While the reason for this is unclear, Song et al., published in vitro data on CaP cell lines that show inhibition of CaP growth at normal physiological androgen levels²⁷. The possibility of TT being beneficial for men with CaP presents an interesting reversal of old axioms, and deserves further research.

The limitations of the present study include its retrospective nature, the limited number of T values following TT onset to determine the physiological effect of treatment, the reliance on clinic notes to determine TT compliance, and the lack of detailed interval PSA values during follow-up with TT.

Conclusion

In testosterone deficient men with a history of treated or untreated CaP, T therapy resulted in increases in serum T levels, with a small but significant increase in PSA. These findings are similar to what is seen in literature currently, and are explained by the saturation model proposed by Morgentaler & Traish^{18,28}. While our rates of BCR were lower than clinical norms, our trial design doesn't allow comment on causative factors.

It is important to recognize the limitations of the retrospective nature of the present study. Future results from randomized controlled trials could lead to a change in our current treatment approach. Until these studies are completed, the use of TT among hypogonadal men with treated CaP or on AS should be monitored closely with serial PSA's, and involve a detailed discussion of the potential risks and benefits with the patient prior to initiation of therapy.

Acronyms & Abbreviations

PSA	Prostate Specific Antigen
CaP	Prostate Cancer
TT	Testosterone Therapy
RP	Radical Prostatectomy
EBRT	External Beam Radiation Therapy
ADT	Androgen Deprivation Therapy
BCR	Biochemical Recurrence
XRT	Radiotherapy

HIFU	High-Intensity Focused Ultrasound
PSAV	Prostate Specific Antigen Velocity
TD	Testosterone Deficiency
Hgb	Hemoglobin
T	Testosterone

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Figure 1.

Bar graph of serum testosterone levels before TT (dark grey) and after TT (light grey) for each treatment modality. Error bars represent 95% Confidence Intervals.

Figure 2.
Line graph of median PSA changes over time while on TT, stratified by risk group.

Figure 3.

PSA after TT initiation in the RP patient group. The N at each time point on the graph represents the number of patients with PSA data at said time point. Average time of last PSA drawn was 50 months. Mean was used in this case as median would result in an undetectable PSA at each time point.

Figure 4.

PSA after TT initiation in the XRT patient group. The N at each time point on the graph represents the number of patients with PSA data at said time point. Average time of last PSA drawn was 39 months.

Figure 5.

PSA after TT initiation in the AS patient group. The N at each time point on the graph represents the number of patients with PSA data at said time point. Average time of last PSA drawn was 32 months.

TT and PSA parameters in 82 patients with CaP classified by primary treatment modality and d'Amico risk stratification.

Table 1

Type of Treatment	D'Amico Risk	n	N receiving neoadj ADT	Time Rx to TT (median months)	Duration TT (median months)	Initial Median T (mmol/L)	Final Median T (mmol/L)	Initial PSA (median)	Final Median PSA	Median PSAV (ng/ml/yr)	BCR (n)
Radical Prostatectomy	All	22	6	15	48	6.60	13.3	undetectable	undetectable	0	none
	Low	3	0	33	55	6.2	11.75	undetectable	0.016	0.0014	none
	Intermediate	11	1	13	37.7	7	15.4	undetectable	undetectable	0	none
	High	8	5	15	59.5	6.25	15.1	undetectable	undetectable	0	none
Radiotherapy	All	50	14	45	36.5	6.25	13.05	0.125	0.18	0.0175	3
	Low	10	3	61	40	7	15.5	0.185	0.145	0.0039	none
	Intermediate	19	6	42	47	6.95	10.6	0.06	0.062	0	1
	High	21	5	43	23	5.6	14.7	0.18	0.49	0.1025	2
Active Surveillance	Low	8	0	n/a	33	5.2	15.5	3.9	5.2	0.51	NA
	HIFU	1	0	4	42	5	1.3	0.26	1.2	0.31	
Cryotherapy	High	1	1	17	9	4.9	NA	1.1	3.2	0.8	