Androgens: Clinical Research and Therapeutics
Volume 3.1, 2022
DOI: 10.1089/andro.2021.0031
Accepted May 17, 2022

Androgens
Clinical Research and Therapeutics
Mary Ann Liebert, Inc. publishers

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An Approach to Testosterone Therapy in Men After Treatment for Localized Prostate Cancer

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Abstract

Testosterone therapy (TTh) is a well-established and safe treatment for men with testosterone deficiency. Historically, great caution has been used in the use of testosterone in men with prostate cancer (PCa) given the pioneering work by Huggins and Hodges showing castration decreased serum acid phosphatase in men with metastatic PCa. For the past several decades new theories including the saturation model have gained traction and as a result the treatment of testosterone deficiency in men with PCa has been transformed. In men treated for localized PCa with prostatectomy a growing body of evidence exists supporting its safety and efficacy in these men. In addition, it has been suggested that TTh may decrease biochemical recurrence. The data are more limited in men treated with radiation and there are no studies currently with a control group. Overall, the body of literature continues to grow suggesting the safety of TTh in well-selected men treated for localized PCa.

Keywords: testosterone deficiency; testosterone replacement therapy; prostate cancer

Introduction

Testosterone therapy (TTh) in hypogonadal males is a well-established and proven standard of care to ameliorate the signs and symptoms of low testosterone, including low libido, low energy, fatigue, decreased muscle mass, and decreased bone density.[1,2]

However, the history of testosterone deficiency and management has long been paralleled by a perennial discussion concerning its complex relationship with prostate cancer (PCa).

Attempts to elucidate the intricacies of the relationship between testosterone and PCa have given rise to a variety of models, the most historically pervasive being the androgen (AR) hypothesis model, first documented in the 1940s by Huggins and Hodges. This hypothesis represents a belief that there is a direct relationship between the level of ARs and the development or acceleration of PCa—a relationship reported by Huggins and Hodges following their findings of PCa regression in men who underwent castration or high-dose estrogen therapy and PCa growth in men given exogenous testosterone.[3] This pioneering research led to a Nobel prize for Huggins in 1966 and also resulted in the twentieth century dominance of the AR hypothesis as a primary informer of clinical decision-making concerning PCa. This work led to the popularization of androgen

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deprivation therapy (ADT), a treatment still employed today in severe or metastatic PCa.

Further studies reporting findings inconsistent with the AR hypothesis prompted the development of the saturation model, which postulated the existence of an AR saturation point, above which testosterone has no influence on the growth of PCa.[4] In 2014, Morgentaler et al. published findings from a double-blind placebo-controlled study, consistent with the saturation model, which demonstrated a lack of significant variation in prostate-specific antigen (PSA) levels in men undergoing testosterone gel therapy, provided their baseline testosterone level was >250 ng/dL.[5] These findings were also supported by a 2013 Rastrelli et al. study that noted minimal impact of increasing testosterone on PSA levels once a concentration of 230–260ng/dL was achieved.[6]

Although there is still much to learn about the relationship between testosterone and PCa, there is currently insufficient data to suggest an increase in PCa risk or recurrence in those undergoing testosterone replacement therapy.[7] However, there remains a United States Food and Drug Administration warning on TTh listing known or suspected PCa as a contraindication. Furthermore, the American Urological Association (AUA) guidelines on testosterone deficiency state there is inadequate evidence to quantify the risk benefit of ratio of TTh in men with PCa.[2] This review aims to provide a better understanding of the literature related to TTh in men treated with radical prostatectomy (RP) or radiation therapy (RT) to allow the clinician the ability to engage in shared decision-making when counseling men with testosterone deficiency and definitively treated PCa.

Methods

The study was deemed IRB exempt. A literature review was performed using PubMed and Google Scholar. The database was searched up until September 2021 and was limited to studies published in English. The literature search included combinations of the following keywords: testosterone, testosterone deficiency, testosterone replacement, testosterone therapy, prostate cancer, localized prostate cancer, radiation therapy, and radical prostatectomy. Cohort studies, prospective studies, review articles, and meta-analyses were included in the analysis. There were no prospective studies identified studying TTh in men with localized PCa. Until recently, TTh in men with PCa was considered contraindicated and this had led to the lack of prospective clinical trials as it was believed to be unethical.

Results and Discussion

Men treated with surgery

RP is an established and effective treatment option for PCa, particularly in men with localized PCa.[8,9] In an aging male population often requiring the use of TTh to relieve the symptoms of testosterone deficiency, men who have undergone RP are no exception. There have been several studies addressing TTh in men who have undergone RP. Kaufman and Graydon were among the first to report on the safety of TTh after RP when, in 2004, they reported no significant side effects in a small group of seven men who had received TTh after RP.[10] Additional studies following this seminal work include a 2009 retrospective study by Khera et al. who reported an increase in testosterone levels (255–459 ng/dL ($p < 0.001$)) with no concurrent increase in PSA levels in hypogonadal men receiving TTh who had undergone RP.[11]

Subsequently, a 2013 retrospective study comparing 103 hypogonadal men receiving TTh after RP and 49 nonhypogonadal men not receiving TTh after RP, reported an increase in PSA from 0.004 to 0.009 ng/mL within the treatment group with a median follow-up of 36 months. However, there was not a statistically significant difference in biochemical recurrence (BCR) (3.9%) defined as PSA >0.2 ng/mL.[12] The AUA guidelines endorse the use of caution in the post-RP initiation of TTh, citing underpowered studies and the potential increase in PSA with post-RP TTh, as reported by Pastuszak et al.[12]

The AUA recommendations state that TTh should only be considered in men who have undergone RP with favorable pathology (e.g., negative margins, negative seminal vesicles, and negative lymph nodes), and who have undetectable PSA.[2] Overall, the current literature supports the safety and efficacy of TTh use in hypogonadal men who have undergone RP.

Not only has the evidence to date shown TTh in men who have undergone RP is a safe and effective treatment, there is also more recent data suggesting TTh may reduce BCR in men who have undergone RP. A 2020 retrospective study by Ahlering et al. explored the relationship between TTh and BCR in men who underwent robot-assisted radical prostatectomy (RARP). They compared 152 patients placed on postoperative TTh after RARP to 419 proportionately matched men with respect to pathological Gleason grade group (GGG) and pathological stage.

These factors are known strong predictors of BCR. Of note, the TTh patient cohort was a well-selected

group with low-risk disease, undetectable PSA levels throughout treatment, symptoms suggestive of testosterone deficiency, low calculated free testosterone (cFT), and delayed post-RP sexual function recovery. After accounting for GGG, pathological stage, preoperative PSA level, and cFT, the authors found that patients in the TTh group were 54% less likely to experience BCR (hazard ratio 0.54, 95% confidence interval 0.292–0.997) at an average of 3.4 years of follow-up. They additionally concluded that in men destined to recur, TTh delayed time to recurrence by an average of 1.5 years.[13]

Although this initially seems counterintuitive, the authors noted that the results appeared consistent with their previous evidence on the connection between low FT levels and increasingly aggressive PCa as well as PCa sensitivity toward metabolic syndrome, diabetes, and obesity.[14,15] They also cited a 2017 population-based study by Loeb et al. reporting a decrease in high-risk PCa in men receiving TTh compared to men not receiving TRT.[16] Therefore, it is logical to conclude that BCR risk may be lower in men receiving TTh due to improved metabolic parameters.[13] Despite limitations, including its retrospective nature, this study introduces a new way of thinking about TTh after RP.

Bernie and Mulhall reported in abstract form the experience of TTh in high-risk PCa patients at Memorial Sloan Kettering Cancer Center.[17] They included men with adverse pathological features, including positive surgical margins, lymph node involvement, seminal vesicle invasion, or Gleason grade ≥8. In their experience they found low testosterone or TTh was not associated with BCR. Although the data are limited and the exact relationship between BCR and TTh remains to be elucidated, the current literature suggests TTh may be safe in patients who have undergone RP including high-risk patients and is not associated with increased risk of BCR. Although not based on high-level evidence, the practice at our institution is to typically wait 3–6 months postoperatively before starting TTh. We also use a shared decision-making approach with the patient and weigh a variety of factors, including postoperative PSA, pathology, and symptoms before starting TTh.

Men treated with radiation

RT for clinically localized PCa is a common treatment with similar efficacy to RP. Despite similar outcomes, there are several distinct differences that are pertinent when considering TTh in these patients. The nature of RT leaving the prostate tissue *in situ* creates at least a theoretical concern of having residual PCa cells that may respond to testosterone. After surgery, the PSA typically becomes undetectable, which is a very clear way of determining BCR. However, after RT, determining BCR is more complex using the Phoenix Criteria where the PSA nadir must first be established.[18,19]

TTh in men with localized PCa treated with RT represents a challenging cohort of patients to study. ADT is often used in combination with RT for men with intermediate- and high-risk PCa and is considered the standard for these patients according to the AUA guidelines.[19] These men are made hypogonadal as part of their cancer treatment and determining the best time to start TTh is complex. These men have testosterone levels below the saturation point and will often see a rise in PSA after initiating TTh.

Furthermore, the initial trials that established the benefit of combination RT and ADT used lower radiation doses than the current standards.[19] Therefore, the current role of ADT in combination with RT for localized prostate therapy is unclear; however, the AUA and National Comprehensive Cancer Network (NCCN) Guidelines do currently recommend combination therapy. Intermediate-risk PCa patients are a heterogenous group making these patients challenging to study, especially in a retrospective nature given the inherent selection bias.

Given these challenges, there are limited studies evaluating the role of TTh in men treated with RT. A recent systematic review found a total of 9 studies all of which were single-arm cohort studies composing a total of 275 men.[20] The lack of any control group makes it difficult to definitively assess the safety of TTh in these patients. The largest single study included 98 men of which three quarters had low or intermediate-risk PCa. In this series 6% of patients had a BCR. The authors concluded that a 6% BCR rate is similar to other published studies using RT for treatment of PCa, thus suggesting TRT is safe.[21] Ory et al. evaluated 50 men who were treated with RT, of which 21 were high risk and 19 were intermediate risk. A total of 14 men received neoadjuvant ADT.

This series found no difference in pre-TTh PSA level when stratified by risk group.[22] Six percent of patients developed a BCR, two with high-risk and one with intermediate-risk disease, which was similar to the BCR rate in the Pastuszak series.[22] Overall it appears,

Table 1. Summary of Studies Evaluating Testosterone in Patients Treated with Radical Prostatectomy for Localized Prostate Cancer

Study	Study type	No. of patients	Follow-up, months	Gleason score of risk group (no. of points)	BCR definition	BCR (%)	Comments
Kaufman et al. (2004)[10]	Case series	7	24	6 (6) 7 (1)	PSA ≥0.1 ng/mL	0	
Agarwal and Oefelein[23]	Case series	10	19	6 (2) 7 (7) 8 (1)	PSA ≥0.1 ng/mL	0	
Khera et al.[11]	Case series	57	13	≤6 (24) 7 (26) 8 (4)	PSA ≥0.1 ng/mL	0	
Pastuszak et al.[12]	Retrospective cohort study	103	27.5	<6 (1) 6.7 (72) ≥8 (9)	PSA ≥0.2 ng/mL	3.9	26 men with high-risk PCa defined as positive margins or nodes or Gleason score >8
Ory et al.[22]	Case series	22	41	NR	PSA >0.2 μg/L with second confirmatory PSA >0.2 μg/L	0	
Bernie et al.[17]	Retrospective cohort study	24	NA	6–7 (18) ≥8 (6)	PSA ≥0.1 ng/mL	46[a]	Only high-risk PCa = Gleason 6–7 with positive surgical margins, lymph node involvement, seminal vesicle involvement or Gleason ≥8 with any pathology status
Ahlering et al.[13]	Retrospective cohort study	152	42	6 (43) 7 (100) ≥8 (9)	Two consecutive PSA values >0.2 ng/mL	7.2	TRT group ∼54% less likely to recur (hazard ratio 0.54, 95% confidence interval 0.292–0.997)

[a]75% BCR in low T with no TRT compared to 46% in low T with TRT ($p = 0.001$).

BCR, biochemical recurrence; NA, not available; NR, not reported; PCa, prostate cancer; PSA, prostate-specific antigen; T, testosterone; TRT, testosterone replacement therapy.

Table 2. Summary of Studies Evaluating Testosterone in Patients Treated with Radiation Therapy for Localized Prostate Cancer

Study	Study type	No. of patients	Follow-up, months	Gleason score or risk group (no. of patients)	BCR definition	BCR (%)	Comments
Pastuszak et al.[21]	Case series	98	40.8	≤6 (47) 7 (28) ≥8 (11)	Absolute nadir +2 ng/mL OR current nadir +3 ng/mL OR 2 consecutive PSA increase >0.5 ng/mL	6.1	
Ory et al.[22]	Case series	50	41	Low (10) Intermediate (19) High (21)	Nadir +2 ng/mL	6	BCR occurred in 2 high-risk and 1 intermediate-risk patient
Morgentaler et al. (2018)[24]	Case series	50	47	NR	Nadir +2 ng/mL	2	
Balbontin et al.[25]	Case series	20	31	2 + 3 (1) 3 + 3 (15) 3 + 4 (3) 4 + 4 (1)	Nadir +2 ng/mL	0	All brachytherapy patients
Pastuszak et al.[26]	Case series	13	29.7	6 (4) 7 (7) 8 (2)	Two consecutive PSA increases >0.5 ng/mL	0	Brachytherapy in 3 and RT in 10. Four patients received ADT with RT
Morales et al.[27]	Case series	5	14.5	3 + 3(2) 4 + 3 (1) 4 + 4 (2)	Nadir +2 ng/mL	0	
Sarosdy[28]	Case series	31	30	5 (3) 6 (19) 7 (6) 8/9 (3)	Nadir +2 ng/mL	0	Heavily weighted with low-risk patients

ADT, androgen deprivation therapy; RT, radiation therapy.

based on small retrospective series, that TTh is safe in well-selected patients treated with RT for localized PCa. TTh use in this group of patients could greatly benefit from larger prospective studies with control groups. To our knowledge there are currently no prospective studies in progress evaluating this topic. We hope prospective studies can be completed in this patient population to more definitively prove the safety and benefits of TTh in patients treated for localized PCa.

As mentioned before, ADT is often given in combination with RT for intermediate- and high-risk PCa. It is prudent for the clinician prescribing TTh to determine if the patient is still receiving ADT as an active treatment for PCa. Despite the paucity of current literature, the practice at our institution is to wait 3 months after completing ADT for shorter 4–6-month courses as is typical with intermediate-risk PCa. We wait 6 months after cessation of ADT when given for a longer duration (1–3 years) for high-risk PCa before initiating TTh.

Conclusion

Overall, the use of TTh in men treated for localized PCa appears safe (Tables 1 and 2). The practice patterns of many urologists are changing in favor of using TTh. However, higher levels of evidence are needed to ultimately prove its safety. Hopefully, we will get to a point with stronger guideline statements in favor of TTh.

Authors' Contributions

All authors contributed to conception, design, writing, and review of the article.

Author Disclosure Statement

A.R. and D.W.B. have no competing financial interests. F.A.Y.: Antares Pharma and Clarus Therapeutics: speaker, Coloplast: advisory board, consultant, Cynosure, Promescent, and Sprout: advisory board, Viome: research grant primary investigator.

Funding Information

No funding was received for this article.

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Cite this article as: Reeves A, Barham DW, Yafi FA (2022) An approach to testosterone therapy in men after treatment for localized prostate cancer, *Androgens: Clinical Research and Therapeutics* 3.1, 174–179, DOI: 10.1089/andro.2021.0031.

Abbreviations Used

ADT = androgen deprivation therapy
AR = androgen
AUA = American Urological Association
BCR = biochemical recurrence
cFT = calculated free testosterone
GGG = Gleason Grade group
PCa = prostate cancer
PSA = prostate-specific antigen
RARP = robot-assisted radical prostatectomy
RP = radical prostatectomy
RT = radiation therapy
TRT = testosterone replacement therapy
TTh = testosterone therapy