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Testosterone Replacement Therapy Reduces Biochemical Recurrence Post-Radical Prostatectomy: Long-term Outcomes

THESIS

submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Muhammed Alaa Moukhtar Hammad

Thesis Committee:
Professor Thomas Ahlering, Co-Chair
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Professor Sheldon Greenfield

2023

DEDICATION

To

my parents Dr. Alaa Mokhtar and Dr. Hala Salama, family, colleagues, and friends

to resilience

"It's the repetition of affirmations that leads to belief. And once that belief becomes a deep conviction, things begin to happen."

Muhammad Ali

and to innovation.

"Medicine is the restoration of discordant elements; sickness is the discord of the elements infused into the living body."

Leonardo da Vinci

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LIST OF ABBREVIATIONS

RP	: Radical prostatectomy
RARP	: Robot-assisted radical prostatectomy
TRT	: Testosterone
BCR	: Biochemical recurrence
PSA	: Prostate-specific antigen
BMI	: Body mass index
p-stage	: Pathological stage
pGGG	: Pathological Gleason Grade Group
DVT	: Deep venous thrombosis
(c)FT	: (calculated) free testosterone
HR	: hazard ratio
SHBG	: sex hormone-binding globulin
PE	: pulmonary embolism
mPca	: metastatic prostate cancer
TT	: testosterone levels

ACKNOWLEDGEMENTS

Dear all,

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As we embark on our future careers, I remain profoundly thankful for the knowledge and skills we have acquired throughout this degree program. May we all strive to implement and apply these learnings to make a meaningful impact in our respective fields.

Once again, I extend my heartfelt appreciation to everyone who has contributed to my academic journey and wish you all continued success in your endeavors.

ABSTRACT OF THE THESIS

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Muhammed Alaa Moukhtar Hammad

Master of Science of Biomedical and Translational Sciences

University of California, Irvine, 2023

Professor Thomas Ahlering, Co-Chair

Associate Professor Faysal Yafi, Co-Chair

Importance: Prostate cancer remains as one of the most common malignancies in men in the United States. Testosterone Replacement Therapy (TRT) is known to improve functional and sexual outcomes in hypogonadal men. TRT historically has been contraindicated for the management of hypogonadism in men with prostate cancer (PC). In 2020, our team demonstrated in a cohort of 850 men that TRT reduced biochemical recurrence (BCR) by 53% (median follow-up 3.5 yrs.). The present study extends the median follow-up time up to 5.84 years [4.18; 7.24].

Objective: This study mainly aims to investigate the utility of TRT to reduce BCR.

Methods: A retrospective review of prospectively collected data between December 2009 and June 2018 undergoing robotic radical prostatectomy by a single surgeon was conducted. 152 patients who had TRT post-RP with a cFT (below 25%) were frequency-matched to 420 patients not receiving TRT with respect to pathological stage (p-stage) and Gleason Grade Group (GGG). Furthermore, the TRT group was propensity-score matched to 304 patients. Propensity scores were calculated using a multivariable logistic model that incorporated the following variables: age, BMI, Gleason group, PSA, SHIM, prostate size, pathological stage, total testosterone (TT), sex hormone-binding globulin (SHBG), and free testosterone (FT). Biochemical recurrence (BCR) was defined as two consecutive prostate specific antigen (PSA) blood tests >0.2 ng/mL. A cox regression model and Kaplan-Meier (KM) graphs were used to analyze rate and time to BCR. We also used our cox regression model of the time to BCR with truncated time of 10.32 to calculate restricted mean survival time (RMST) for the TRT vs no-TRT groups.

Results: With propensity-score matching, there were no baseline differences in demographics observed except in TT (p-value= <0.001), cFT (p-value <0.001), and follow-up time (p-value = 0.004). In the cox regression multivariate analysis of the propensity-scored matched control, patients with a higher calculated free testosterone were less likely to have a BCR (p-value= 0.013). In the same analysis, patients with a higher GGG, p-stage, and preoperative PSA (p-value= <0.001) were more likely to have a BCR. Patients receiving TRT had 47% reduction in BCR rates (p-value = 0.011) after a median follow-up time of

5.84 [4.18;7.24] years. Furthermore, our 10-year cox regression model for the time to BCR showed RMST difference between the TRT and no-TRT groups: in patients who did recur, patients on TRT had an increased latency of 0.44 years.

Conclusion and Relevance: With the long-term follow-up, TRT was observed to have a continuing protective effect in preventing and delaying BCR in patients post-RARP when compared to patients who did not receive TRT.

I. INTRODUCTION

Prostate Cancer

Prostate cancer is the most common cancer affecting men in the United States, excluding non-melanoma skin cancers.[1] The projected estimates for 2023 suggest approximately 288,300 new cases of prostate cancer and about 34,700 deaths attributed to the disease.[1] This cancer's incidence rate experienced a decline between 2007 and 2014 due to changes in screening recommendations, but since 2014, it has seen an annual increase of about 3% overall and around 5% for advanced-stage prostate cancer.[1]

Epidemiological trends reveal shifts in the incidence of metastatic prostate cancer (mPCa) over the years. Between 2010 and 2018, there was a 41% increase in mPCa incidence in men aged 45 to 74 and a 43% increase in those older than 75.[2] This cancer is also a significant cause of death globally, ranking as the second most common cancer diagnosis in men and the fifth leading cause of death worldwide.[3]

Prostate-specific antigen (PSA) is a significant protein produced by normal prostate cells and plays a crucial role in prostate health. Elevated PSA levels in the serum may indicate prostate cancer, although it is not a definitive diagnostic test.[4] The management of clinically localized prostate cancer involves a complex decision-making process considering risk factors, patient preferences, and available treatment options.[5] Management strategies encompass active surveillance, prostatectomy, radiation therapy, hormone therapy, and chemotherapy, with prognosis dependent on the disease's stage.[5]

In general, prostate cancer is highly prevalent among older males in the United States, with PSA testing being a pivotal tool for early detection. The increasing incidence of mPCa highlights the need for continued monitoring and research. The management of this cancer is multifaceted, considering various treatment options to balance efficacy and quality of life for patients with localized disease.

Testosterone and Radical Prostatectomy: Friends or Foes

While none of the prostate cancer guidelines recommend routine measurement of testosterone levels (TT), sex hormone-binding globulin (SHBG), and calculated free testosterone (cFT), Huynh et al. convincingly demonstrated that while TT remain relatively constant over decades, a notable and significant reduction occurs in cFT level per decade, necessitating taking both into consideration.[6–9] The observed link between low cFT levels and heightened PCa aggressiveness, along with an elevated risk of post-treatment recurrence, underscores the critical role of systematic cFT assessment in PCa patients. While TRT appears supported for men with low-risk disease and erectile dysfunction, its prophylactic application, though conceptually intuitive and physiologically substantiated, likely necessitates randomized trials for validation.

While testosterone (TT) levels have historically been assumed to naturally decline with age, Huynh et al's investigation of PCa patients contradicts this belief, revealing that TT levels remain relatively stable as men age, with a marginal change of < 1% over each decade.[6] In contrast, a distinct decline in cFT levels—approximately ~12% per decade—

primarily driven by SHBG, becomes evident. They emphasized the necessity of testosterone screening encompassing both SHBG and cFT measurements.

Within the context of PCa, a pivotal finding of the study revolves around the inverse relationship observed between low cFT levels and escalating PCa aggressiveness. Specifically, individuals with cFT values in the lowest quartile face an elevated risk—ranging from 1.2 to 3.2 times—of developing highly aggressive (Grade Group 5) cancer, Extracapsular Extension (EPE), and Seminal Vesicle Invasion (SVI). Additionally, following surgical intervention, those displaying low cFT levels also experience a 30% heightened risk of BCR, even after accounting for equivalent disease characteristics.

Considering the ongoing hesitations surrounding TRT in PCa patients, questions arise concerning the menacing potential of low cFT levels. Notably, recent reports suggest that TRT in individuals with low cFT levels could serve as a protective measure against PCa incidence, severity, and recurrence.[10–12] A population-based study by Loeb et al. in 2017 involving 38,570 patients demonstrated a reduction in high-risk PCa cases among those receiving TRT compared to untreated counterparts.[11] Similarly, Lopez et al. published data from insurance claims databases further supporting the inverse relationship between hypogonadism and PCa incidence.[13] Extending these findings, the earlier follow-up of this study revealed a 53% reduction in BCR among 152 men undergoing TRT compared to 419 untreated and risk-matched controls over a median of 3.6 years.[14] Moreover, even among individuals poised for recurrence, concerns about testosterone exacerbating aggressiveness are refuted by our results, which show that TRT leads to a reduction in PSA doubling time and delays recurrence by an average of 1.5 years.[14] It is therefore of

importance to prioritize the identification and monitoring of men with low cFT levels, particularly when considering TRT for individuals with low-risk disease and poor recovery of sexual function, despite undetectable PSA levels in PCa.

Specific Aims

To investigate whether TRT will still delay BCR after a longer follow-up time of our cohort, we will utilize BCR and the time to BCR as our primary outcome measures. Using retrospective data, this study will focus on the following specific aims:

Primary Aim: Inspect the long-term outcomes of TRT on Pca and whether it will still delay BCR and be consistent with our published early follow-up data. We hypothesize that administering TRT will continue to have a protective effect with longer follow-up time.

Secondary Aim: Observe any cardiovascular events occuring to both the control and intervention groups.

II. METHODS

Patient Population, Data Collection, and Follow-Up

This study constitutes a long-term follow-up of a previously published retrospective case-control investigation.[14] The research focuses on men who were prescribed testosterone replacement therapy (TRT) after robotic-assisted radical prostatectomy (RARP). Over the period from December 2009 to June 2018, a total of 850 consecutive patients underwent RARP as the primary localized prostate cancer treatment under the supervision of a single surgeon. Excluding patients undergoing cytoreductive RP (three cases), simple prostatectomy (nine cases), or those with missing data (two cases), the analysis comprised a cohort of 836 patients. Pre- and postoperative levels of total TT, SHBG, and cFT were assessed in both the TRT and control groups. The cFT was determined prospectively using a validated online calculator. These values, alongside oncological and pathological variables, were collected and anonymized in an electronic database under an Institutional Review Board protocol at the University of California, Irvine. The study adhered to the Health Insurance Portability and Accountability Act, and the data collection process adhered to Federal Guidelines for informed consent.

Within the cohort, 152 patients (18.2%) received TRT after RARP. Rigorous tracking of TRT status occurred during follow-up visits within the established database. Patients eligible for TRT had primarily demonstrated pathologically confirmed low- to intermediate-risk cancer with Gleason Grade Group (GGG) 1-3, undetectable PSA levels (<0.05 ng/mL), low baseline and/or 3-month postoperative cFT levels (<5.7 ng/mL), and potential erectile function recovery issues. These individuals received comprehensive

information to comprehend the physiological benefits and risks associated with TRT. Rigorous follow-up involved regular PSA measurements at each visit (at intervals of 1-3 months), with discontinuation of TRT if PSA levels exhibited suggestive increases. The administration of TRT included daily application of testosterone cream to the forearm area. Subsequent evaluations, occurring 3 months after TRT initiation and every 6 months thereafter, encompassed testosterone, PSA, hematocrit, and hemoglobin levels. The TRT dosage was adjusted to maintain levels within physiological limits while remaining above the median. Potential cardiovascular side effects were assessed through patient-reported surveys in both cohorts.

The primary outcome measures included biochemical recurrence (BCR), defined as two consecutive PSA values >0.2 ng/mL, and the corresponding time to BCR, measured from RARP to the occurrence of the first of two PSA values exceeding the threshold. Comparison and analysis encompassed BCR rates and adjusted time to BCR between the TRT and control groups. To compare our long-term outcomes before and after propensity score-matching, we had 2 control groups: a frequency-matched group and a propensity score-matched group. The frequency-matched cohort was used by our earlier published follow-up.[14] The selection of participants for this control group followed a process of frequency matching in respect to pathological GGG and pathological stage, both recognized as influential risk factors for BCR. This matching procedure was conducted without knowledge of oncological outcomes and was subsequently validated by an independent third party. A total of 420 control patients, not undergoing TRT, were included in the comparative analysis (Figure 1). Our propensity-score matched control group had 304 patients.

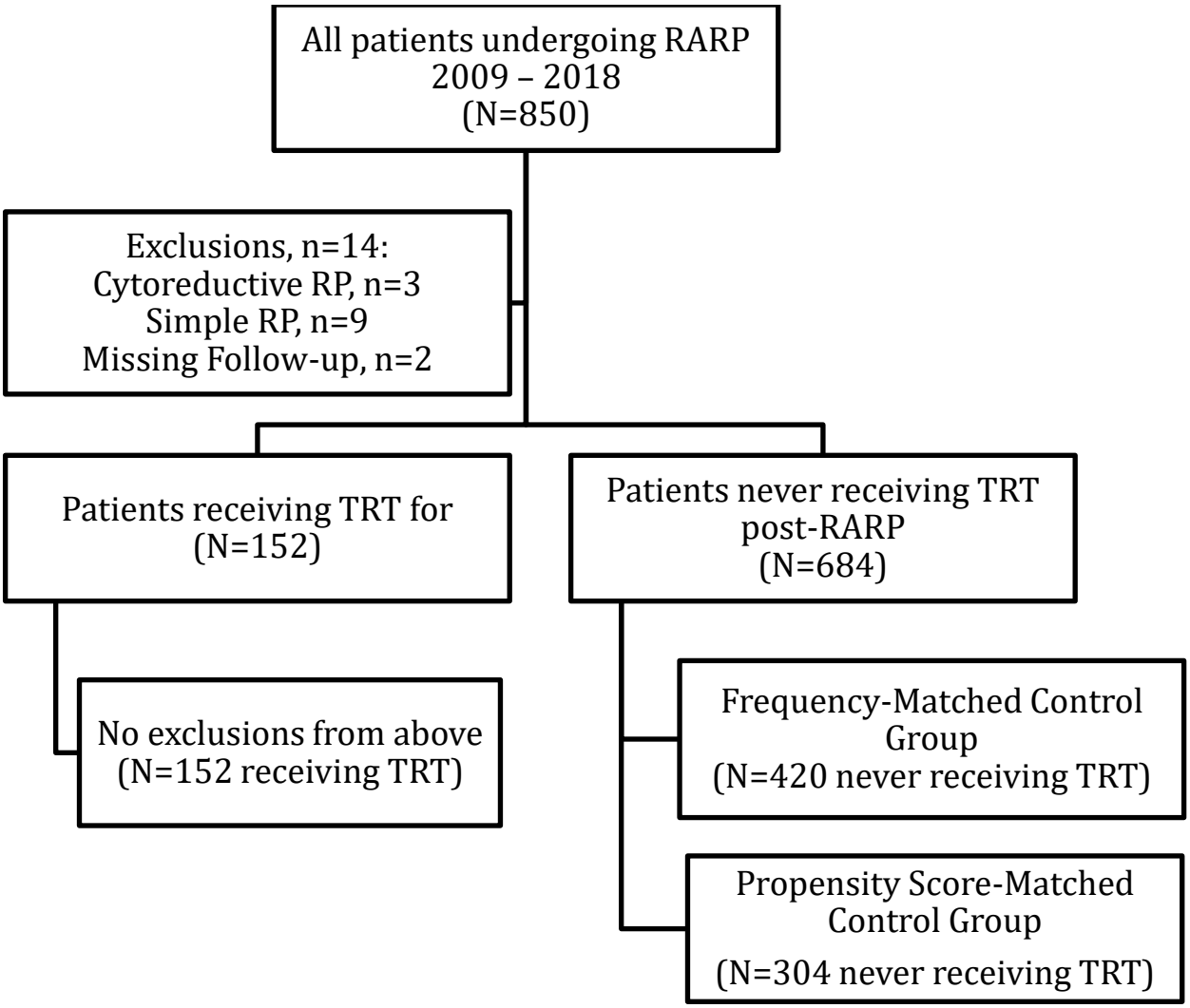

Figure 1*. Flowchart depicting patient selection process.*

Statistical Methods and Analysis

Statistical Analysis

The statistical analyses were conducted using the R software (version 4.2.0) and R Studio (version 2023.06.0+421). To evaluate the differences in baseline patient and disease-specific parameters between the groups undergoing testosterone replacement therapy (TRT) and those not receiving TRT, we employed appropriate statistical methods. Specifically, for categorical variables, we utilized chi-square tests, while for continuous variables, we applied independent t-tests. These methods enabled us to compute descriptive estimates of the observed differences in these parameters between the two groups.

Survival Analysis for Biochemical Recurrence

To assess the potential impact of testosterone replacement therapy on BCR, we employed advanced survival analysis techniques. The Kaplan-Meier (KM) method was utilized to estimate the median and interquartile range (IQR) of survival probabilities from the index date for both the TRT and no TRT groups. For patients who did not experience BCR, their data were censored at the date of their last follow-up. The Cox proportional hazards regression was then applied to compute hazard ratios (HRs) along with corresponding 95% confidence intervals (CIs). This enabled us to quantify the association between testosterone replacement therapy and the risk of experiencing BCR. Furthermore, to compare the survival outcomes between the TRT and no TRT groups, we employed the restricted mean survival time (RMST) methodology with truncated time of 10.32 years.

Propensity Score-Matched Analysis

To address potential selection bias and confounding factors, we conducted a propensity score-matched analysis. Propensity scores were calculated using a multivariable logistic model that incorporated relevant variables such as age, BMI, Gleason group, PSA, SHIM, prostate size, pathological stage, total testosterone (TT), sex hormone-binding globulin (SHBG), and free testosterone (FT). This process ensured that patients receiving TRT were appropriately matched with those not receiving TRT in a 1:2 ratio using nearest neighbor matching without replacement. By doing so, we minimized the influence of potential covariates on treatment assignment. Subsequently, we performed a comprehensive comparison of patient characteristics and outcomes before and after the propensity score matching procedure.

These meticulous analyses were carried out to provide robust insights into the potential effects of testosterone replacement therapy on BCR risk, while also considering and mitigating the potential biases that might arise from patient characteristics. The results of these analyses are instrumental in contributing to a more comprehensive understanding of the relationship between testosterone replacement therapy and BCR risk in our patient population.

Statistical Methods and Analysis

Statistical Analysis

The statistical analyses were conducted using the R software (version 4.2.0) and R Studio (version 2023.06.0+421). To evaluate the differences in baseline patient and disease-specific parameters between the groups undergoing TRT and those not receiving TRT, we employed appropriate statistical methods. Specifically, for categorical variables, we utilized chi-square tests, while for continuous variables, we applied independent t-tests. These methods enabled us to compute descriptive estimates of the observed differences in these parameters between the two groups.

Survival Analysis for Biochemical Recurrence (BCR)

To assess the potential impact of testosterone replacement therapy on BCR, we employed advanced survival analysis techniques. The Kaplan-Meier (KM) method was utilized to estimate the median and interquartile range (IQR) of survival probabilities from the index date for both the TRT and no TRT groups. For patients who did not experience BCR, their data were censored at the date of their last follow-up. The Cox proportional hazards regression was then applied to compute hazard ratios (HRs) along with corresponding 95% confidence intervals (CIs). This enabled us to quantify the association between testosterone replacement therapy and the risk of experiencing BCR. Furthermore, to compare the survival outcomes between the TRT and no TRT groups, we employed the restricted mean survival time (RMST) methodology.

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III. RESULTS

Patient Demographics

In comparison to the frequency- matched control group, the 152 patients placed on TRT, all exhibited low preoperative total testosterone and levels and/or experienced delayed sexual function recovery. Additionally, these patients maintained undetectable PSA levels at median follow-up time of 5.84 [4.18, 7.24] years. Notably, cFT levels were significantly elevated above the cohort's normal median of 4.88 [3.90; 6.14] ng/mL (p-value= <0.001), leading to the resolution of symptoms reported by the patients.

A comparison of the frequency-matched control group demographic characteristics and those of the TRT group were detailed in Table 1. The TRT and control groups demonstrated comparability in terms of age, preoperative PSA level, pathological stage, and Gleason Grade Group (GGG) preoperative IIEF-5 score. However, the following were significantly higher in the control group: body mass index (BMI), SHBG (p-value= <0.001), testosterone (TT) (p-value= <0.001), and cFT (p-value= <0.001) levels. Time to BCR was significantly higher in the group receiving TRT.

	No TRT N=420	TRT N=152	P-value
Adjusted PSA	5.50 [4.38;8.05]	5.65 [4.39;7.93]	0.852
Age	62.0 (7.18)	61.4 (7.91)	0.424
BMI	26.5 [24.6;28.7]	27.1 [25.6;30.3]	0.012
Adjusted SHIM	23.0 [18.0;25.0]	22.0 [17.0;25.0]	0.273
Prostate Weight	50.7 [42.0;66.7]	51.0 [43.8;64.0]	0.456
Gleason group:			0.989
1	124 (29.5%)	43 (28.3%)	
2	207 (49.3%)	77 (50.7%)	
3	64 (15.2%)	23 (15.1%)	
4	8 (1.90%)	2 (1.32%)	
5	17 (4.05%)	7 (4.61%)	
P-Stage Adjusted:			1.000
pT2	361 (86.0%)	131 (86.2%)	
pT3	59 (14.0%)	21 (13.8%)	
P-Stage numerical:			1.000
1	361 (86.0%)	131 (86.2%)	
2	58 (13.8%)	21 (13.8%)	
3	1 (0.24%)	0 (0.00%)	
Total Testosterone	357 [278;441]	263 [214;343]	<0.001
SHBG	42.0 [31.5;55.0]	37.0 [25.0;48.0]	<0.001
Free Testosterone	5.88 [4.66;7.34]	4.88 [3.90;6.14]	<0.001
Time to FU	5.04 [2.99;6.91]	5.84 [4.18;7.24]	0.002
Time to BCR	1.97 [0.57;3.87]	3.94 [2.41;6.03]	0.019
BCR:			0.676
0	357 (85.0%)	132 (86.8%)	
1	63 (15.0%)	20 (13.2%)	

Table 1. Demographics of patients receiving TRT vs frequency-matched control not receiving TRT

In comparison to the propensity-score matched control group, the 152 patients placed on testosterone replacement therapy (TRT), all exhibited low preoperative total testosterone and levels and/or experienced delayed sexual function recovery. Additionally, these patients maintained undetectable PSA levels at median follow-up time of 5.84 [4.18, 7.24] years. Notably, cFT levels were significantly elevated above the cohort's normal median of 4.92 [3.96; 6.18] ng/mL (p-value= <0.001), leading to the resolution of symptoms reported by the patients.

After propensity-score matching, the demographic characteristics of the 2 groups were detailed in Table 2. The TRT and control groups demonstrated robust comparability in terms of age, preoperative PSA level, pathological stage, Gleason Grade Group (GGG), preoperative IIEF-5 score, follow-up duration, SHBG, and body mass index (BMI). However, a significant difference was observed in testosterone (TT) (p-value= <0.001) and cFT (p-value= <0.001) levels, which were significantly higher in the control group.

	No TRT N=304	**TRT N=152**	**P-Value**
Adjusted PSA	5.50 [4.30;8.12]	5.65 [4.39;7.93]	0.949
Age	61.2 (7.24)	61.4 (7.91)	0.793
BMI	26.9 [25.1;29.5]	27.1 [25.6;30.3]	0.462
Adjusted SHIM	23.0 [18.0;25.0]	22.0 [17.0;25.0]	0.355
Prostate Weight	51.5 [42.6;67.2]	52.0 [44.3;64.0]	0.845
Gleason Group	2.00 [1.00;2.00]	2.00 [1.00;2.00]	0.805
Adjusted p-stage :			0.728
pT2	267 (87.8%)	131 (86.2%)	
pT3	37 (12.2%)	21 (13.8%)	
P-Stage numerical:			0.701
1	267 (87.8%)	131 (86.2%)	
2	36 (11.8%)	21 (13.8%)	
3	1 (0.33%)	0 (0.00%)	
Total Testosterone	320 [252;378]	264 [216;357]	<0.001
SHBG	38.9 [30.0;48.0]	37.0 [25.8;47.9]	0.146
Free Testosterone	5.69 [4.52;6.90]	4.92 [3.96;6.18]	<0.001
Time to Follow-up	5.06 [3.05;6.91]	5.84 [4.18;7.24]	0.004
Time to BCR	2.56 [0.54;4.44]	3.94 [2.41;6.03]	0.068
BCR:			0.740
No	259 (85.2%)	132 (86.8%)	
Yes	45 (14.8%)	20 (13.2%)	

Table 2. Demographics of patients receiving TRT vs propensity score-matched control not receiving TRT

Biochemical Recurrence

In table 1, descriptive analysis of 152 patients on TRT and 420 frequency-matched controls, revealed that 13.2% and 15.0% of patients had BCR, respectively. The Cox proportional hazards regression analysis showed that TRT was an independent predictor of recurrence-free survival. (Table 3) Gleason Grade Group (GGG), pathological stage, and preoperative PSA levels were also significant predictors of BCR. (Table 3) (Figure 2)

	Univariate				Multivariable		
Characteristic	N	HR	95% CI	p-value	HR	95% CI	p-value
Adjusted PSA	566	1.08	1.06, 1.10	<0.001	1.07	1.05, 1.10	<0.001
Gleason group	567						
1-4		—	—		—	—	
5		5.68	3.19, 10.1	<0.001	5.18	2.88, 9.33	<0.001
P-Stage Adjusted	567						
pT2		—	—		—	—	
pT3		3.11	1.94, 4.98	<0.001	2.77	1.71, 4.49	<0.001
FT	547	0.91	0.82, 1.01	0.074	0.91	0.82, 1.01	0.082
Real TRT	567						
No TRT		—	—		—	—	
TRT		0.7	0.42, 1.16	0.164	0.54	0.31, 0.93	0.025

HR = Hazard Ratio, CI = Confidence Interval

Table 3. Cox proportional hazards regression analysis of patients receiving TRT vs frequency-matched control not receiving TRT.

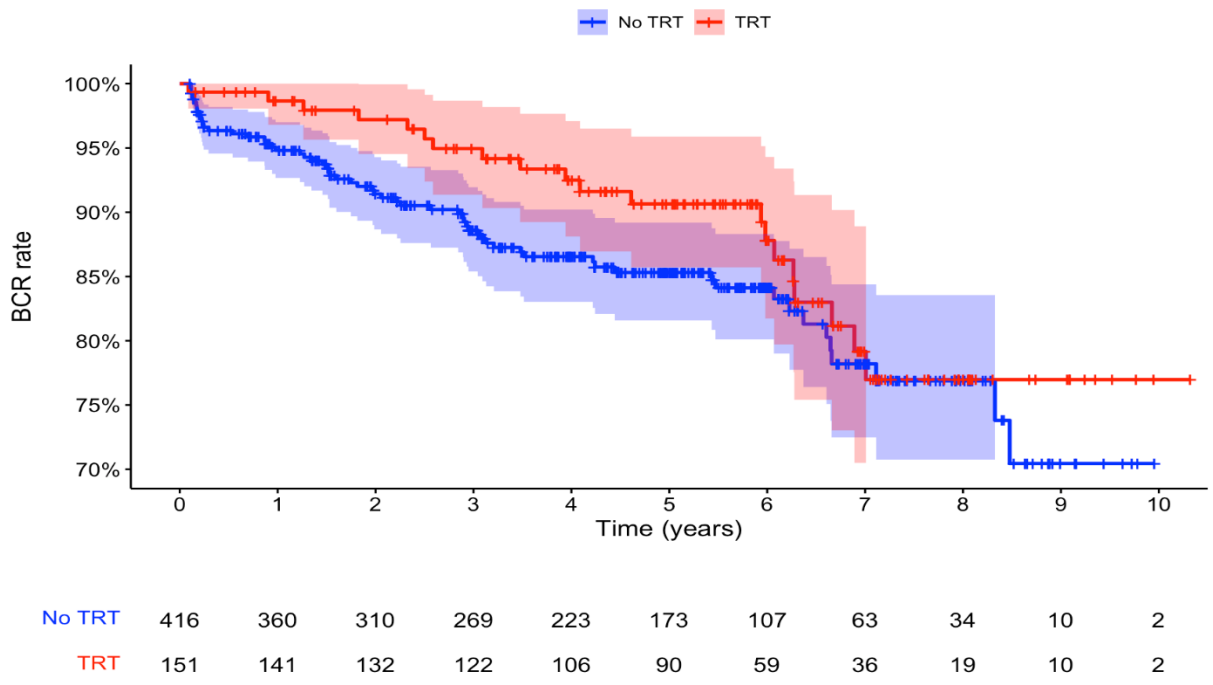

Figure 2. Kaplan Meier Estimates of BCR rates in patients receiving TRT vs frequency-matched control not receiving TRT.

In table 2, the descriptive analysis of the TRT group versus propensity-score matched controls, revealed that 13.2% and 14.8% of patients had BCR, respectively. Through Cox proportional hazards regression analysis, TRT again emerged as an independent predictor of recurrence-free survival. This prediction was further underscored by an approximate 47% reduction in the risk of BCR on the multivariate analysis (HR 0.47, 95% CI 0.27–0.84) observed across a median follow-up time of 5.84 [4.18; 7.24] years (Table 4). Beyond TRT, Gleason Grade Group (GGG), pathological stage, and preoperative PSA levels also emerged as significant predictors of BCR (Figure 3). Additionally, using the cox regression models for both the TRT and no TRT groups, the restricted mean survival time (RMST) was calculated to compare survival between the 2

groups with the truncation time set to 10.32 years, which is the minimum duration of the most observed time to BCR in both groups. The RMST of BCR was estimated to be 8.83 in the TRT group compared to 8.39 years in the no-TRT group. Thus, we can infer with this approximately 10-year model that TRT was able to delay BCR by 0.44 years in patients destined to recur.

	Univariate				Multivariable		
Characteristic	N	HR	95% CI	p-value	HR	95% CI	p-value
Adjusted PSA	451	1.08	1.05, 1.11	<0.001	1.07	1.04, 1.10	<0.001
Gleason group	451						
1-4		—	—		—	—	
5		5.06	2.58, 9.95	<0.001	5.44	2.73, 10.8	<0.001
Adjusted pStage	451						
pT2		—	—		—	—	
pT3		3.51	2.05, 5.99	<0.001	2.7	1.53, 4.76	<0.001
Free Testosterone	451	0.82	0.71, 0.94	0.005	0.84	0.74, 0.96	0.013
Real TRT	451						
No TRT		—	—		—	—	
TRT		0.69	0.41, 1.18	0.175	0.47	0.27, 0.84	0.011

HR = Hazard Ratio, CI = Confidence Interval

Table 4. Cox proportional hazards regression analysis of patients receiving TRT vs propensity-matched control not receiving TRT.

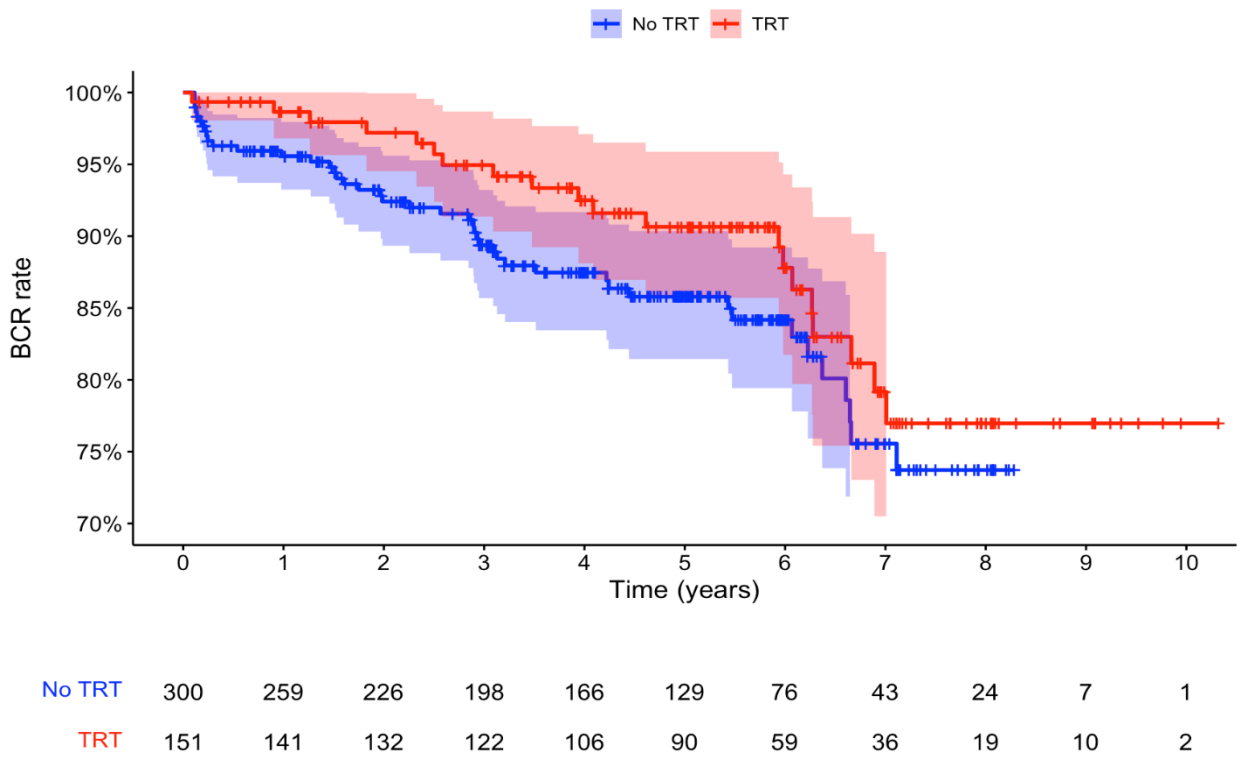

Figure 3. Kaplan Meier Estimates of BCR rates in patients receiving TRT vs propensity-matched control not receiving TRT.

Cardiovascular Events

The assessment of side-effects and cardiovascular events included the distribution of electronic questionnaires to the participants, with a response rate of 23.43% (134 out of 572). 43 patients who responded out of the 152 patients who had TRT reported no advent of any cardiovascular events including but not limited to heart attack, DVT/PE, stroke, angina pectoris, hypertension, palpitations, and irregular beats. The results were consistent with the original findings of the early follow-up.[14]

IV. DISCUSSION

In this study, we aimed to investigate the long-term outcomes of using TRT to patients who have undergone RP with time to BCR as our primary outcome measure. The safety of using TRT in patients who have undergone RP for localized prostate cancer is a topic of significant interest and ongoing research. Various studies have contributed to the understanding of the potential risks and benefits of TRT in this patient population.

A systematic literature review and meta-analysis conducted by Parizi et al. aimed to evaluate the oncological safety of TRT in prostate cancer patients who had undergone definitive local therapy with curative intent. The study conducted a comprehensive literature search using databases such as PubMed, Scopus, Web of Science, and Cochrane Library. The pooled BCR rate in prostate cancer patients treated with TRT after definitive local therapy was analyzed using a random effects model. The results of this meta-analysis provided valuable insights into the association between TRT and BCR in prostate cancer patients who had undergone curative intent therapy. The findings suggested that TRT may not be associated with an increased risk of BCR in these patients, providing important evidence regarding the oncological safety of TRT in the context of prostate cancer treatment.[15]

Furthermore, an updated review of literature by Natale et al. discussed the evolving perspective on testosterone therapy after prostate cancer treatment. Historically, testosterone therapy was contraindicated in men with a history of prostate cancer due to concerns about potential cancer growth. However, recent evidence has challenged this

notion, indicating that testosterone therapy might not necessarily lead to prostate cancer growth, particularly in men definitively treated for non-mPCa. This review highlighted the changing understanding of the relationship between testosterone therapy and prostate cancer and emphasized the importance of evidence-based decision-making in the treatment of hypogonadal men with a history of prostate cancer.[16]

Additionally, studies such as the one conducted by Sarkar et al. analyzed large national cohorts to assess the safety of testosterone replacement therapy after RP for localized prostate cancer. The results indicated that there were no significant differences in clinical T stage, post-RP PSA levels, or hormone therapy between patients who received testosterone replacement therapy and those who did not. These findings further contribute to the growing body of evidence suggesting that testosterone replacement therapy might be administered to prostate cancer patients post-RP without significant adverse effects on BCR, prostate cancer-specific survival, or overall survival.[17]

The safety of using testosterone replacement therapy in patients who have undergone radical prostatectomy for localized prostate cancer has undergone a significant evolution over the years. Earlier concerns about the potential for testosterone therapy to fuel prostate cancer growth have been challenged by our study demonstrating the oncological safety of TRT in this patient population and in fact showing delaying of BCR by 47%. Furthermore, our 10-year cox regression model demonstrated that in patients who did recur, patients on TRT had an increased latency of 0.44 years. Our findings along with

recent meta-analyses and cohort studies have shown that TRT may not be associated with an increased risk of BCR in prostate cancer survivors after definitive local therapy.

As for our secondary outcome, no cardiovascular events or other related adverse events were reported with TRT usage for approximately 5 years of follow-up. The cardiovascular safety to use TRT was also demonstrated in the recent findings of the The Testosterone Replacement Therapy for Assessment of Long- term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial.[18] In a multicenter, randomized, double-blind, placebo-controlled, non-inferiority trial, a total of 5246 men aged 45 to 80 years, who either had preexisting cardiovascular disease or were at a high risk of it, and reported symptoms of hypogonadism, were enrolled. These participants had fasting testosterone levels of less than 300 ng per deciliter. The study aimed to assess the cardiovascular safety of testosterone-replacement therapy. The participants were divided into two groups: one receiving daily transdermal 1.62% testosterone gel with dosage adjustments to maintain TT between 350 and 750 ng per deciliter, and the other receiving placebo gel. The primary cardiovascular safety endpoint was the occurrence of any component of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, analyzed using a time-to-event approach. A secondary cardiovascular endpoint was defined as the occurrence of any component of a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, also analyzed using a time-to-event approach. The study found that testosterone-replacement therapy did not increase the risk of major adverse cardiovascular events (MACE) in comparison to the placebo group. There was no

significant difference in the occurrence of the primary cardiovascular endpoint between the two groups (7.0% in the testosterone group and 7.3% in the placebo group) (HR 0.96, 95% CI 0.78-1.17, P<0.001 for noninferiority). However, the testosterone group did exhibit increased risks of acute kidney injury and pulmonary embolism when compared to the placebo group. It's noteworthy that testosterone therapy was associated with improved sexual function and anemia correction over two years but had no effect on diabetes progression or glycemic parameters.

These findings provide clinicians with valuable information when considering the use of TRT in hypogonadal men with a history of prostate cancer who have undergone RP. It is important to note that while the mounting evidence suggests a more favorable safety profile for TRT in this context, individual patient characteristics and clinical considerations should always guide treatment decisions. The evolving understanding of the relationship between testosterone therapy and prostate cancer underscores the need for ongoing research to further elucidate the benefits and potential risks of TRT in this specific patient population.

Limitations

One drawback of this study is its retrospective design. Despite the thorough patient selection criteria, there remains the potential for both selection bias and information bias. Given the absence of random group assignments, decisions to undergo TRT are subjective.

Furthermore, another constraint pertains to our secondary outcome, which is the low response rate to patient-reported outcomes related to adverse events. Nevertheless, within the context of our study, our earlier follow-up published study and the recent TRAVERSE trial findings substantiate our observations.

In addition, there are limitations of propensity-score matched studies. Such studies lack the ability to account for hidden or unmeasured confounding variables that could impact both treatment allocation and outcomes. While propensity score matching strives to create comparable groups based on observable factors, it cannot address the effects of unobserved elements that might still introduce bias into the estimated treatment effects. This limitation holds relevance when latent variables or unmeasured traits are associated with both treatment assignment and the outcome of interest. Despite efforts to balance observed factors, propensity score matching cannot eliminate the potential for residual bias due to unobserved confounders.

Future Directions

Additional research is imperative to gain deeper insights into the potential impact of TRT on the BCR delay. This necessitates the execution of larger, more extensive, and multi-center investigations. By doing so, the limitation stemming from the current study's randomization issue can be directly tackled. Moreover, these endeavors would facilitate comprehensive analyses, enabling a more robust understanding of the subject matter. Furthermore, the current study's findings serve as a crucial steppingstone for forthcoming research avenues. These forthcoming endeavors have the potential to harness cutting-edge statistical and computational tools, seamlessly incorporating artificial intelligence (AI) and machine learning (ML) techniques. This integration would equip researchers with the means to dissect intricate datasets of substantial magnitude and intricacy, leading to the construction of multidimensional models. Unlike traditional statistical methodologies, these models can discover intricate patterns that might otherwise remain elusive for certain patient cohorts for instance. It is worth noting that the infusion of AI and ML capabilities introduces the prospect of patient-centric modeling. This innovative approach holds the promise of yielding patient-specific prognostications. As a result, the application of such methodologies could substantially elevate the precision of treatment outcomes assessment and decision-making processes. This marks a pivotal advancement in the medical landscape, where tailored and optimized therapeutic interventions can be designed based on individual patient characteristics.

In general, an indispensable opportunity exists for more extensive investigations into the potential implications of TRT in delaying BCR. The expansion into larger scale

randomized multi-center studies not only addresses prevailing limitations but also allows for more comprehensive insights. Furthermore, the current study's groundwork paves the way for future research endeavors, leveraging advanced AI and ML tools. This integration has the potential to reshape the landscape of medical research, ushering in an era of personalized treatment strategies guided by intricate predictive models.

V. SUMMARY AND CONCLUSIONS

In this study, we investigated the impact of TRT usage following RP. The results of the study revealed a significant reduction in BCR rates among individuals who underwent TRT. Moreover, for those individuals who were destined to experience recurrence, TRT was associated with a significant delay in the time it took for BCR to occur. TRT has traditionally been avoided in prostate cancer patients due to concerns about potentially accelerating the disease. However, the novel insights gleaned from this study challenge this conventional belief, raising new hypotheses and underscoring the necessity for comprehensive, multi-center randomized controlled trials.

These long-term results strongly warrant further exploration. Initiation of extensive multi-center randomized controlled trials, which would provide a more comprehensive understanding of the therapeutic potential of TRT in this specific context is crucial. By unraveling the complexities of TRT's impact on BCR and recurrence timelines, these trials have the potential to revolutionize treatment paradigms and enhance the quality of life for prostate cancer patients.

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