THE JOURNAL of UROLOGY®
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Original Clinical Article

Testosterone Therapy in Men After Radical Prostatectomy for Organ-Confined, Low-Intermediate Prostate Cancer

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Purpose: Testosterone therapy (TTh) in men with T deficiency who have undergone radical prostatectomy (RP) for prostate cancer remains controversial. We aimed to assess the impact of TTh on biochemical recurrence (BCR) rates after RP in men with low-intermediate organ-confined disease.

Materials and Methods: This study included men who underwent an RP at our institution for organ-confined prostate cancer and had grade groups 1 to 3 on RP pathology. A Cox model was created for time to BCR with T use included as a time-dependent covariate, adjusted for age, preoperative PSA, grade group at RP, and the presence of comorbidities. A landmark analysis was used: Patients were included in the analysis if their last PSA in the 18 weeks postoperatively was undetectable and they had not had BCR or been lost to follow-up by that point, and follow-up for BCR began at 18 weeks. BCR was defined as a PSA $\geq$ 0.1 ng/mL after RP with a second confirmatory rise $\geq$ 0.1 ng/mL.

Results: The study population included 5199 men after RP, with 198 patients receiving T at any point after RP and 5001 not receiving T. The median age was 59 (IQR, 55-65) and 61 (IQR, 56-66) years, respectively. Men in the T group tended to present with more vascular comorbidities. For those receiving T, clomiphene citrate was prescribed in 49% of men, 32% received transdermal T, and 19% intramuscular T. We found a nonsignificantly decreased risk of BCR associated with the use of T after RP (HR, 0.84; 95% CI, 0.48-1.46; $P = .5$), and overall rates of BCR were low, with probability of BCR at 5 years less than 2% in both groups.

Conclusions: TTh can be given to select men after RP. We found no evidence that administration of TTh after RP causes BCR.

Key Words: low testosterone, prostate cancer, testosterone therapy

Submitted April 3, 2024; accepted September 20, 2024; published 000.

Funding/Support: Sidney Kimmel Center for Prostate and Urologic Cancers and the NIH. National Cancer Institute to Memorial Sloan Kettering Cancer Center through the Cancer Center Support Grant (P30 CA008748).

Conflict of Interest Disclosures: The Authors have no conflicts of interest to disclose.

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Rates of both prostate cancer (PC) and testosterone deficiency (TD) increase markedly with age and thus often coexist. However, the standard treatment for TD, testosterone therapy (TTh), is contraindicated in men with PC, based on the labeling for all testosterone (T) products. Starting with the seminal article by Huggins and Hodges in 1941 demonstrating that PC is hormone-dependent,[1] T has been thought to "add fuel to the fire," resulting in concerns that the use of TTh after radical prostatectomy (RP) would cause biochemical recurrence (BCR). More recently, the

https://doi.org/10.1097/JU.0000000000004267
Vol. 00, 1-6, January 2025
Printed in U.S.A.

T saturation model has challenged this notion.[2] At low levels of T, increases in PC cell exposure to T lead to cell proliferation. Above a certain serum T threshold, likely varying from patient to patient but believed to be in the 150 to 250 ng/dL (5.2-8.7 nmol/L) range, the androgen receptor is maximally stimulated, and further increases in T levels have no additional prostate cell proliferative effect.[2-4] However, TTh in men with TD who have undergone RP remains controversial because most of the data to date are supported only by small-sized studies, without long-term follow-up, and still, the persistent concern among patients and healthcare providers that T will increase the risk of recurrence after treatment.

Low T levels are associated with physical, sexual, psychocognitive, and metabolic effects, leading to a reduction in overall health and quality of life.[5,6] Very low T levels ($\leq$200 ng/dL, 6.9 nmol/L) are associated with an increased risk of bone mineral density loss, glycemic control issues (diabetes), major adverse cardiovascular events, and premature death.[5-9] Denying TTh to men with TD, therefore, is potentially associated with serious medical consequences. For those with lower-risk PC, it seems plausible that these harms might outweigh those associated with an increase in cancer risk caused by TTh. At our institution, we have, therefore, selectively given TTh to men with TD and lower-risk PC.

In this study, we aimed to assess the impact of TTh on BCR rates after RP in men with low-intermediate organ-confined disease.

METHODS

Study Population

After obtaining institutional review board approval, we identified men who underwent RP at our institution between January 2006 and June 2023, had organ-confined PC (no seminal vesical involvement, negative surgical margins, negative extracapsular extension, and no lymph node involvement), and had Gleason grade groups 1 to 3 on surgical pathology.[10]

TTh

The initiation of T after surgery was a shared decision between physician and patient. TTh was offered to patients who had low T (defined as $<$ 300 ng/dL) and symptoms of T deficiency and who had an undetectable PSA as early as 3 months after surgery. These patients were counseled regarding the potential risks, benefits, and the absence of long-term safety data on TTh in men after RP. TTh modality selection was based on a given patient's baseline luteinizing hormone levels (defining candidacy for clomiphene citrate [CC]), patient concerns about testicular atrophy with exogenous TTh, risk of T transference with gel/cream use, use of anticoagulant medication for intramuscular TTh candidates, patient preference, and cost to the patient. Patients were prescribed a form of TTh selected from the following modalities: transdermal (gels/creams, patch), intramuscular T cypionate injection (IMT), or CC. Patients on TTh had T and PSA levels checked 2 weeks after commencing transdermal TTh and 4 weeks after starting IMT or CC and at these same intervals after any dose adjustment.

Once a patient was on a stable TTh dose, T monitoring labs (including PSA and hematocrit) were checked every 6 months. Symptomatic response was evaluated at a time point no sooner than 4 months after TTh commencement. Patients who did not see an improvement in their TD symptoms at this time point had TTh discontinued (unless their baseline total T levels were $\leq$ 200 ng/dL or they had unexplained osteoporosis or unexplained elevation in HbA1c). For this study, it was assumed that patients remain on TTh for the study period. TTh was stopped if BCR occurred. BCR was defined as a PSA $\geq$ 0.1 ng/mL (at a time point $\geq$ 42 days after RP) with a subsequent confirmatory PSA $\geq$ 0.1 ng/mL.[11] Time to BCR was defined as the time to first PSA measurement $\geq$ 0.1 ng/mL for patients with BCR and the time to last PSA measurement for patients without BCR.

Statistics

As our cohort of interest is patients who are at risk of BCR after RP, we first needed to identify this cohort for analysis. Being at risk of BCR requires an undetectable PSA measurement after RP. Because PSA measurements after RP can be taken at different times, we used a landmark analysis to account for this. The typical clinical pathway for postsurgery follow-up has patients returning for a PSA test approximately 3 months after surgery. We investigated several landmarks ranging between 12 and 18 weeks and found that using an 18-week landmark allowed us to include the largest possible cohort of men on T while reducing the number of patients who would be excluded because of BCR events occurring before the landmark. Patients were eligible to be included in the cohort if their last PSA before the 18-week landmark was $<$ 0.1 ng/mL and they had known follow-up after the landmark date. Our goal was to assess whether the use of TTh after RP was associated with an increased risk of BCR.

We aimed to investigate potential differences in BCR rates between those who were on TTh and those who were not. Because differences could be due to TTh causing BCR, or due to different levels of baseline risk between patients who received TTh and those who did not, we created a Cox proportional hazards model where the predictor of interest was TTh, adjusting for age at surgery, preoperative PSA, grade group at surgery, and the presence of 5 comorbidities (diabetes, obstructive sleep apnea, high cholesterol, hypertension, and coronary artery disease). Because patients could begin TTh at any point starting 3 months after surgery, TTh was included in the model as a time-dependent covariate. Patients were considered to be in the no-TTh group starting from the postsurgery landmark until the start of their TTh and then considered to be in the TTh group until BCR diagnosis or last follow-up. Because T use was time-dependent, we compared patient and disease characteristics by creating univariable Cox proportional hazards

models for the outcome of time from landmark to T initiation or last follow-up. We also present descriptive statistics separately for those who started testosterone within 2 years of RP and those who did not. All analyses were conducted using R version 4.3.0 with the tidyverse (v2.0.0) and gtsummary (v1.7.2) packages (R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021).[12,13]

RESULTS

Patient Population

There were 5960 men who met our eligibility criteria. We excluded 145 patients who did not have a recorded PSA measurement after surgery; 33 who started T before surgery and patients who either had no PSA measurement within 18 weeks after surgery (N = 143) or had PSA $\geq$ 0.1 ng/mL on their last measurement before the landmark (N = 51). Among the 51 patients with PSA $\geq$ 0.1 ng/mL at last measurement, there was 1 BCR event identified. An additional 389 men had no PSA measurement after the landmark leaving 5199 patients in the cohort. Of the 5199 men who had RP for organ-confined PC, 198 men initiated TTh any time between surgery and the date of BCR or last PSA measurement. Of the 198 men receiving TTh, the median age at commencement of TTh was 62 years (IQR, 57-67). The distribution of TTh modalities included CC 49%, IMT 19%, and transdermal T 32%. The median duration of TTh for men who did not have BCR was 3.4 years (IQR, 1.7-5.9). We also present descriptive statistics on patients with at least 2 years of follow-up separately by those who started testosterone within 2 years and those who did not (Supplementary Table 1, https://www.jurology.com). Differences identified between these groups were consistent with the results of our Cox regression analyses. Rates of obstructive sleep apnea (18% vs 37%, $P < .001$) and hypertension (44% vs 60%, $P < .001$) were higher among patients who started TTh within 2 years postoperatively. There was a nonsignificant difference in diabetes rates between the 2 groups (non-TTh group 9%, TTH group 14%; $P = .052$). Data on presurgery T levels were missing for a large number of patients, but as would be expected, patients who started TTh within 2 years after RP had lower levels of presurgery testosterone. We also found patients starting TTh within 2 years were more likely to have undergone robotic surgery (76% vs 55%).

BCR

There were 310 BCR events with a median follow-up time from the 18-week landmark for those without BCR of 35 months (IQR, 15-58). Rates of BCR at 5 years after the landmark were as expected, very low in this group of men with lower-grade organ-confined disease: 2% in those taking TTh (95% CI, 0%-4%) and 2% in those not taking T (95% CI, 1%-3%). Table 1 summarizes the BCR rate at 10 years based on the pathological Gleason grade group and TTh vs no TTh. We found a nonsignificantly decreased risk of BCR associated with the use of T after surgery (HR, 0.84; 95% CI, 0.48-1.46; $P = .5$), although the CI is wide, given the small cohort of patients on TTh and the very low rates of BCR in this cohort, and excludes a potentially clinically important increase in risk (Table 1). However, we did find that patients taking TTh had higher baseline risks of BCR, with increased PSA and higher rates of GGG3 disease, meaning that any residual confounding would bias these patients toward having higher recurrence rates, whereas our results found lower recurrence rates for these patients. We did not proceed to an interaction analysis because there was no significant association between TTh and BCR. It can also be mentioned that despite the more limited follow-up and events from 5 to 10 years (Figure), it is shown that BCR rates are higher in the no-TTh group during this period.

Because TTh is time-dependent, we compared patient and disease characteristics by creating univariable Cox proportional hazards models for time from landmark to TTh or last follow-up (Table 2). There was some evidence that patients who were older at the time of surgery had a decreased hazard of starting TTh (HR, 0.91 per 5 years; 95% CI, 0.83-1.00, $P = .059$) and that patients with Gleason grade group 3 had an increased hazard (HR, 1.68; 95% CI, 1.07-2.65; $P = .052$), although these did not meet conventional levels of statistical significance. Patients who had diabetes (HR, 2.01; 95% CI, 1.37-2.93; $P < .001$), obstructive

Table 1. *Rates of BCR at 10 y With 95% CIs for Those Taking Testosterone vs Not Taking Testosterone, Separately by the Pathologic Gleason Grade Group, Along With the Estimates for Testosterone Use From the Cox Model for BCR. The Estimate for Grade Group 1 Patients on Testosterone is Based on Only 1 BCR Event*

Grade group	No testosterone	Testosterone	HR	95% CI	*P* value
1	5.2% (1.5%-8.8%)	15% (0%-37%)	0.84	0.48-1.46	.5
2	16% (12%-20%)	8.9% (0.2%-17%)			
3	40% (27%-51%)	32% (7.2%-50%)			

Abbreviation: BCR, biochemical recurrence.

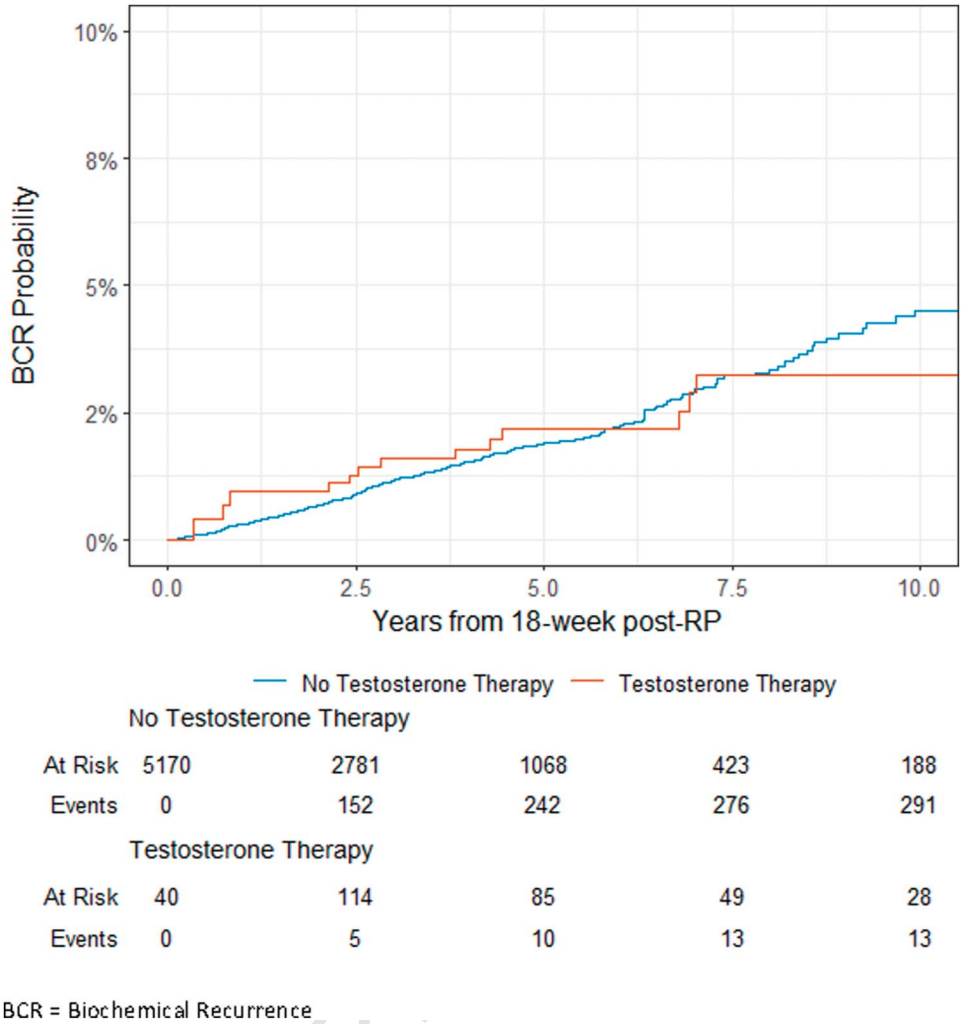

Figure. Adjusted survival curve showing BCR event rates by group, accounting for the time-dependent nature of testosterone therapy, $P = .5$. BCR indicates biochemical recurrence; RP, radical prostatectomy.

sleep apnea (HR, 2.53; 95% CI, 1.88-3.40; $P < .001$), hypertension (HR, 1.66; 95% CI, 1.25-2.19; $P < .001$), or high cholesterol (HR, 1.33; 95% CI, 1.00-1.75; $P = .048$) had increased hazard of starting TTh, as well those patients having 2 or more comorbidities (HR, 2.13; 95% CI, 1.61-2.82; $P < .001$). Patients with higher presurgery PSA also had an increased hazard of starting TTh, although the effect was relatively small (HR, per 1 ng/mL 1.02; 95% CI, 1.01-1.03; $P = .002$). We hypothesized that this is likely because both the use of postoperative TTh for these patients and the use of robotic surgery have become more common in recent years. To test this hypothesis, we repeated the analysis for surgery type adjusting for date of surgery and found that there was no longer a significant difference (HR, 1.34; 95% CI, 0.87-2.06; $P = .066$).

DISCUSSION

In this study, which included the largest sample size reported and the optimal methodology to analyze TTh in this selected group of men with organ-confined PC and grade groups 1 to 3 on surgical pathology, we found no evidence that administration of TTh after RP causes BCR. TTh appears to be safe in this highly specific population and does not appear to be a factor associated with BCR during short-term and medium-term follow-up. Although our 95% CI indicates a HR of close to 1.5, such a relative risk would not be clinically relevant because of the very low overall risk of BCR among these patients. It is possible that our multivariable models did not account for all confounders. However, we believe any residual confounding would not affect our conclusions. We found that patients on TTh had higher baseline risks, which would bias these patients toward higher recurrence rates, whereas our results show nonsignificantly lower recurrence rates in this group, indicating that confounding does not explain our results. The excellent oncologic outcome for this group of men suggests that the benefits of T might possibly

Table 2. *Association Between Patient and Disease Characteristics and Testosterone Therapy Use. Because Testosterone Therapy Use is a Time-Dependent Covariate, Estimates are Generated From Univariable Cox Proportional Hazards Models for Time From Landmark to Initiation of Testosterone Therapy or Last Follow-Up*

Characteristic	N	HR	95% CI	*P* value
Age at RP (per 5 y)	5199	0.91	0.83-1.00	.059
Race	4995			.13
Asian		—	—	
Black		3.71	0.88-15.7	
Other		4.74	0.92-24.4	
White		2.91	0.72-11.7	
Diabetes	5199	2.01	1.37-2.93	< .001
Obstructive sleep apnea	5199	2.53	1.88-3.40	< .001
Hypertension	5199	1.66	1.25-2.19	< .001
High cholesterol	5199	1.33	1.00-1.75	.048
Coronary artery disease	5199	1.23	0.67-2.26	.5
≥2 comorbidities	5199	2.13	1.61-2.82	< .001
Pre-RP PSA (per 1 ng/mL)	5182	1.02	1.01-1.03	.002
Pre-RP testosterone (per 50 ng/dL)	1826	0.77	0.72-0.82	< .001
RP type	5199			.001
Open		—	—	
Laparoscopic		0.90	0.55-1.46	
Robotic		1.64	1.14-2.37	
Pathologic Gleason grade group	5199			.052
1		—	—	
2		1.08	0.75-1.56	
3		1.68	1.07-2.65	

Abbreviation: RP, radical prostatectomy.

outweigh its potential harms. Nonetheless, TTh in this population should still be conducted under rigorous guidance and monitoring, with strict PSA and T-level follow-ups and ongoing communication with the uro-oncological team.

These data are consistent with the saturation model, where the androgen receptor on PC cells is maximally stimulated at serum T levels in the 150 to 250 ng/dL range. The vast majority of men (76%) in this analysis had pre-TTh serum T levels above the saturation point, median 282 (203-314) ng/dL; thus, we would expect no change in PSA, at least early on after RP.

Athough the literature lacks robust, long-term safety data, there have been numerous small case series evaluating the use of TTh in men after surgery,[14-20] with no indication that TTh in men after surgery for low-intermediate grade PC is associated with an increased risk of BCR. These studies have historically been small, with sample sizes between 7 and 152 men after surgery compared with a control group size between 49 and 1256 men. Of the 3 studies reporting follow-up duration, a median follow-up after surgery was between 27 and 48 months. All these studies described no differences in rates of BCR in men on TTh compared with control groups. The BCR rates in these studies ranged between 4% and 7% for the TTh groups vs 12% and 16% for the control groups. The absence of a difference in BCR rates between treatment and control groups reported by other studies is similar to our findings. GG and preoperative PSA levels have been reported as predictors of BCR,[15,18] with one study even suggesting that TTh was an independent predictor of BCR-free survival.[15] We did not find TTh as a predictor of BCR on multivariable analysis.

The main limitation of our study is that we only have a medium-term follow-up. It is possible that longer term exposure to T might eventually lead to growth of quiescent PC cells sufficient to cause recurrence. Strengths of our study include a large series of patients, rigorous T testing for TTh patients, and use of a rigorous BCR definition: Most of the prior studies had used a BCR definition of PSA levels between 0.2 and 0.4 ng/mL, which was significantly higher than the 0.1 ng/mL definitions used in this study. Our study is the largest series in the literature to date, but further research including larger numbers of patients receiving TTh with extended follow-up would add support to our conclusions.

CONCLUSION

TTh can be given to select men after RP. Longer-term outcome needs to be assessed. Consideration should be given to including higher risk patients in research studies on postprostatectomy TTh.

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