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Testosterone Therapy in Men with Biochemical Recurrence and Metastatic Prostate Cancer: Initial Observations

Abraham Morgentaler,[1,*,i] Alejandro Abello,[1,ii] and Glenn Bubley[2]

Abstract

Introduction: Although prostate cancer (PCa) has long been considered an absolute contraindication for testosterone therapy (TTh), growing literature suggests TTh may be safely offered to men with localized PCa. We here present a single-center series of men treated with TTh for relief of symptoms, despite having more advanced disease, namely biochemical recurrence (BCR) or metastatic PCa (MET).

Methods: We identified men treated with TTh with BCR, MET, or adjuvant androgen deprivation therapy (ADT). Consent included risks of rapid PCa progression and death. Laboratory and clinical results were analyzed.

Results: Twenty-two men received TTh: 7 with BCR, 13 with MET, and 2 with adjuvant ADT. Median age was 70.5 years (range 58–94). Median TTh duration was 12 months (range 2–84) overall, including 20 months for BCR and 9.5 months for MET. Mean serum testosterone (T) increased from 210 to 1111 ng/dL. Median PSA (interquartile range) increased from 3.1 ng/mL (0.2–4.5) to 13.3 ng/mL (3.4–22) in the BCR group, 6.3 ng/mL (1.2–31) to 17.8 ng/mL (6.2–80.1) in the MET group, and <0.1 to 0.3 ng/mL in the ADT group. All patients reported symptom relief, especially improved vigor and well-being. Overall mortality was 13.6% and PCa-specific mortality was 4.5% during the period of TTh and 6 months after discontinuation. Seven of 10 with follow-up imaging within 12 months showed no progression. Five men have died: three during TTh and two succumbed at 2 years or longer after discontinuing TTh. One of the three deaths during TTh was PCa-specific. Three men developed significant bone pain at 7–41 months; two discontinued TTh and one continued, after focal radiation. There were no cases of rapid-onset complications, vertebral collapse, or pathological fracture.

Conclusions: These initial observations indicate TTh was not associated with precipitous progression of PCa in men with BCR and MET, suggesting a possible role for TTh in selected men with advanced PCa whose desire for improved quality of life is paramount.

Keywords: testosterone; prostate cancer; testosterone therapy; testosterone and prostate diseases; androgen deprivation therapy; hormone replacement therapy; metastatic prostate cancer and testosterone

Introduction

The diagnosis of prostate cancer (PCa) has been considered an absolute contraindication for testosterone (T) therapy (TTh) for decades, based on the belief that TTh "activates" PCa growth, first asserted by Huggins and Hodges.[1] In 1981, Fowler and Whitmore reported that 45 of 52 men with metastatic PCa who received testosterone demonstrated an "unfavorable

[1]Division of Urology, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.
[2]Division of Hematology and Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.
[i]ORCID ID (https://orcid.org/0000-0002-5925-4086).
[ii]ORCID ID (https://orcid.org/0000-0001-8302-2763).

*Address correspondence to: Abraham Morgentaler, MD, 200 Boylston Street, #309, Chestnut Hill, MA 02467, USA, Email: amorgent@bidmc.harvard.edu

response" within 30 days.[2] Since standard treatment for advanced PCa is to lower serum T with androgen deprivation therapy (ADT), it seemed logical that raising serum T promotes PCa growth. For these reasons it has been widely believed that raising testosterone is likely to cause rapid disease progression, morbidity, and death in men with PCa.

However, a growing literature has challenged this concept. Multiple case series have demonstrated low rates of PCa progression or recurrence in men after radical prostatectomy (RP),[3,4] radiation therapy,[5] and in men on active surveillance.[6,7] Population-based studies have failed to show that use of TTh is associated with worse PCa outcomes.[8] The apparent paradox whereby ADT causes disease regression in PCa yet TTh appears to not cause worse PCa outcomes is resolved by the saturation model,[9] describing a growth curve in which maximal androgenic stimulation of PCa is achieved at low serum T concentrations, with little to no additional stimulation occurring at higher serum T concentrations. There is extremely limited evidence regarding saturation in advanced PCa, consisting of absence of prostate-specific antigen (PSA) progression with TTh in a case report,[10] and an inverted U-curve in PCa cell lines *in vitro* exposed to progressively increasing androgen concentrations, with maximal growth achieved at near-physiological concentrations followed by growth inhibition at higher concentrations.[11] However, positive results from the use of bipolar androgen therapy (BAT) in men with castrate-resistant PCa,[12] and a modified BAT protocol (mBAT)[13] indicate that elevating serum testosterone is not necessarily harmful.

Whereas there has been growing evidence for the benefits of TTh in the general population of men with testosterone deficiency,[14] and moderate experience in men with PCa after definitive local therapy or with low-risk disease on active surveillance, there is scant published experience with use of TTh in men with nonlocalized PCa in clinical practice. We present in this study our initial observations of TTh in a set of men with advanced PCa treated with TTh. These men all specifically sought TTh, for a number of reasons, including prior experience with TTh, adverse experience with ADT, or belief that a robust serum T concentration would be beneficial for their health despite known concerns that TTh would hasten PCa growth.

Methods

We identified all men in the database at Men's Health Boston treated with TTh and with biochemical recurrence (BCR), metastatic PCa (MET), or who were treated with ADT for high risk of recurrence after definitive local treatment through end of June 2020. One man presented initially with BCR and eventually developed metastases: his results are included in both the BCR and MET groups for the relevant periods. Treatment with TTh was initiated in all cases at the patient's request to improve or optimize quality of life. All patients underwent extensive counseling and signed a consent form indicating their awareness that treatment could cause rapid disease progression, with associated morbidity and death. Relevant data were collected for PCa disease status and prior treatment. BCR was defined as PSA >0.2 ng/mL after surgery, or nadir +2 ng/mL after radiation or high-intensity focused ultrasound (HIFU).

All men in the study had previously consulted with an oncologist or urologist specializing in PCa and were aware of standard PCa-specific treatment options. All patients specifically requested TTh, many because of previous experience with TTh or due to symptoms that arose from ADT. There was no requirement to obtain psychological counseling. One patient with MET on ADT with bothersome sexual symptoms first underwent surgical placement of a penile prosthesis to address his erectile dysfunction. There was no protocol in place for cessation of TTh, although men understood they could discontinue treatment at any time and for any reason. Coordination of care was attempted whenever possible with local oncologists or urologists; however, in many cases patients were advised by their local physicians that they would not participate in a treatment regimen that included TTh. At each visit men affirmed they wished to continue with TTh, or it was discontinued.

Men were considered candidates for TTh if they had suggestive symptoms and total testosterone was <350 ng/dL or free testosterone <100 pg/mL. Treatment consisted of injections of testosterone cypionate at doses ranging from 100 to 200 mg weekly or in more recent years at high-dose treatment of 200–400 mg every 2 weeks. High-dose injections were used in the MET group based on data suggesting supraphysiological T concentrations may suppress PCa growth[11] and after publication of results of BAT in men with metastatic castrate-resistant PCa.[12] Topical gels and subcutaneous pellets were also used in standard doses to maintain normal serum T concentrations, and dosage was adjusted to optimize clinical response. An mBAT protocol was used in selected

men with MET, consisting of repeated 12-week cycles during which high-dose (400 mg) testosterone cypionate intramuscular injections were given every 2 weeks for a total of 8 weeks, followed by 4 weeks of daily oral enzalutamide 80–160 mg.[13] None of the men in the MET group had castrate-resistant disease.

Monitoring for the BCR group included PSA at 3 months intervals for the first year, and then every 6 months. For MET group on TTh alone, PSA was obtained every 3 months, and for the mBAT group PSA was obtained every 3 months at the end of 4 weeks of antiandrogens. Follow-up imaging studies were obtained at 6-month intervals in men with MET, and at least annually in BCR. Follow-up for local patients was performed in the office every 3 months for the first year and then at least every 6 months. For patients living at a distance, follow-up visits were in person when possible, and through televisits at other times. Subjective response to treatment was based on structured discussions that addressed energy, mood, strength, and sexuality. No validated questionnaire was used.

The Memorial Sloan Kettering Cancer Center online tool was used to calculate PSA doubling times (https://www.mskcc.org/nomograms/prostate/psa_doubling_time). Prostate cancer-specific (PCS) mortality was defined as deaths occurring as a result of PCa during TTh or within 6 months of discontinuation of TTh. Overall mortality was defined as deaths from any cause during the period of TTh or within 6 months of its discontinuation.

Statistical analysis

We compared and summarized findings from BCR and metastatic groups. Medians and interquartile ranges (IQRs) were used to describe continuous variables based on small sample size and non-normally distributed variables. Ranges were presented for selected results. Percentages and proportions were used to describe categorical variables. We compare continuous variables between groups using Wilcoxon rank sum tests, and a p-value <0.05 was set to determine statistical significance. We used Stata 15® to perform the statistical analysis of the data. This study is reported under IRB # 2010-P-000241 from Beth Israel Deaconess Medical Center.

Results

Between 2005 through June 2020 a total of 22 men with advanced PCa received TTh, with 15 of these treated within the past 5 years. The study group comprised 13 men with MET, 7 men with BCR, and 2 men treated with adjuvant ADT after radiation deemed high risk. For the entire group, the median age at TTh initiation was 71 years (range 58–94), median PSA was 2.52 (range 0.01–546), median Gleason score was 7 (range 6–9), and median baseline testosterone was 204 ng/dL (range 3–629). The median duration of TTh was 12.5 months (range 2–84). Duration of TTh was 6 months or greater in 19 men. Baseline characteristics for the BCR and MET groups are presented in Table 1, and individual case details, including response to TTh, are shown in Table 2. For the entire group, PCS mortality was 4.5% and overall mortality was 13.6%. Results for the BCR and MET groups are presented in Table 3.

BCR group

Median age for the seven men in the BCR group was 69.5 years (range 59–85). Primary treatment was RP in three and radiation therapy in four. Treatment of the radiation group was external beam radiotherapy (XRT) alone in two men, brachytherapy in one. One additional man first underwent two treatments with HIFU, followed by XRT when PSA continued to rise. Two of three men with BCR after RP developed rising PSA despite additional treatment with radiation. The third developed BCR 9 years after RP and did not

Table 1. Baseline Characteristics by Group

	BCR = 7	Metastatic = 14
Median age (IQR)	69.5 (59–85)	72.0 (66–74)
Median PSA (IQR)	3.14 (0.2–4.5)	4.1 (0.3–31)
Primary PCa treatment (%)		
Unknown	0%	7.7%
Brachytherapy	14.3%	0%
External beam radiation therapy	28.6%	23.1%
External beam radiation+HIFU	14.3%	7.7%
RP		
Proton therapy	42.9%	23.1%
ADT only	0%	7.7%
	0%	30.8%
Bone metastases (%)		
Yes	0%	71.4%
No	100%	28.6%
Nodal metastases (%)		
Yes	0%	50%
No	100%	50%
ADT (%)		
Yes	14.3%	50.0%
No	85.7%	50.0%
mBAT		
Yes	0%	57.1%
No	100%	42.9%

ADT, androgen deprivation therapy; BCR, biochemical recurrence; HIFU, high-intensity focused ultrasound; IQR, interquartile range; mBAT, modified BAT protocol; PCa, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy.

Table 2. Case Details

Age (years)	Disease status	Duration TTh (months)	Initial PCa Rx	Metastatic disease burden	Prior TTh	Hx ADT	Response to TTh	Comments
70	Met	14	Proton Tx	High	N	Y	Weakness improved and personality returned	Continues on TTh. Increased uptake bone scan without new lesions at 1 year
74	Met	10	ADT	Low	Y	Y	Strength, vigor, sexual function improved, and personality returned	Myocardial infarction at 6 months, died during TTh at 10 months from peptic ulcer disease
61	Met	41	RP	Low	N	N	Strength and sexuality improved	Discontinued TTh at 41 months due to increased hip pain, worsened bone scan
94	Met	11	ADT	High	N	Y	Strength and cognition improved	Died during TTh
76	Met	4	XRT	High	N	Y	Strength and vigor improved with TTh	Urinary retention at 3 months. Discontinued TTh on advice of local MD
68	Met	2	None	Low	N	N	Strength and vigor improved with TTh	Discontinued TTh on recommendation of local MD
73	Met	8	ADT	Low	N	Y	Vigor, walking, and sexual function improved	Continues TTh. New bone lesions at 10 months
75	Met	9	RP	High	N	Y	Vigor improved	Continues on TTh. XRT to new pelvic adenopathy at 6 months
63	Met	24	XRT	Low	N	Y	Strength improved and personality returned	Discontinued TTh when PNBx showed residual cancer
72	Met	8	ADT	High	N	Y	Strength and vigor improved	Discontinued TTh when needed XRT for back pain/metastases
71	Met	4	RP	Low	N	N	Strength, well-being, and sexuality improved	Continues on TTh. Bone scan unchanged at 12 months
60	Met	7	XRT	Low	Y	Y	Sense of well-being improved	TTh discontinued for rising PSA
66	Met	84	ADT	Low	N	Y	Sexual function and vigor improved	Died of myelofibrosis after 7 years TTh
67	Met	41	HIFU	Low	Y	Y	Strength and libido improved	Discontinued TTh when developed bone marrow replacement by PCa
59	BCR	63	RP	NA	Y	N	Vigor, mood, libido, and well-being improved	Continues on TTh
65	BCR	16	HIFU/XRT	NA	Y	Y	Strength, vigor, and libido improved	Bone metastases noted at 16 months, continued TTh
58	BCR	33	RP	NA	Y	N	Vigor and well-being improved	Discontinued TTh when PSA reached 20 ng/mL
61	BCR	48	RP	NA	Y	N	Well-being, strength, and sexual function improved	Continues on TTh
85	BCR	20	XRT	NA	N	Y	Cognition improved	Discontinued TTh when PSA reached 22 ng/mL
74	BCR	13	Brachy	NA	Y	N	Well-being and vigor improved	Continues on TTh
75	BCR	5	XRT	NA	N	Y	Cognition improved	Continues on TTh
69	Adjuvant ADT	16	XRT	NA	N	Y	Cognition improved	Continues on TTh without metastases
77	Adjuvant ADT	12	XRT	NA	N	Y	Well-being and vigor improved	Discontinued TTh on recommendation of local MD

TTh, testosterone therapy; XRT, external beam radiotherapy.

Table 3. Baseline and Follow-Up Variables While on Testosterone Therapy Between Metastatic and Biochemical Recurrence Groups

	BCR = 7	Metastatic = 14
Median baseline PSA, ng/dL (IQR)	3.1 (0.2–4.5)	6.3 (0.3–31)
Median follow-up PSA, ng/dL (IQR)	13.3 (3.4–22)	17.8 (6.2–80.1)
Median increase in PSA, ng/dL (IQR)	13.3 (2.8–19)	7.5 (2.35–83.7)
Median baseline T, ng/dL (IQR)	264 (202–470)	181 (21–333)
Median follow-up T, ng/dL (IQR)	1062 (980–1076)	1011 (724–1500)
Median increase in T, ng/dL (IQR)	613 (585–874)	879.5 (591–1241)
Median baseline hematocrit, % (IQR)	45.6 (39.2–49.5)	42 (40.5–44.2)
Median follow-up hematocrit, % (IQR)	46.5 (42–48.2)	47.2 (41.7–49.25)
Median hematocrit change, % (IQR)	−0.9 (-1.3–0.90)	4.8 (2.4–5.9)
Duration of TTH (IQR)	20 (13–48)	9.5 (7–24)

T, testosterone.

receive pelvic XRT. Five had previous experience with TTh for a diagnosis of T deficiency before developing BCR. None were castrate at time of initiation of TTh.

Baseline median PSA was 3.1 ng/mL (range 0.2–8.2 ng/mL). Median duration (IQR) of TTh was 20 months (13–48), and median (IQR) increase in PSA after TTh was 13.3 (2.8–19). Median PSA (IQR) doubling time was 8.9 months (7.1–14.0). One man with BCR developed metastases after 16 months of TTh with a baseline PSA of 32 ng/mL after two HIFU treatments for Gleason 8 disease. No other complications were observed in this group during TTh. One died of metastatic PCa 6 years after discontinuing TTh when his PSA exceeded 20 ng/mL after 33 months of TTh. Four men continue on TTh for up to 5 years without evidence of metastases, with a mean duration of 32.5 months. Overall and PCS mortality were 0% in this group.

MET group

Median age for the 14 men in the MET group was 72 years (range 60–94), and baseline median PSA was 6.3 ng/mL (range <0.1–546). Seven had bone metastases, three had pelvic adenopathy, and four had both. Five of the men with bone metastases had high disease burden. Seven men presented while on ADT and/or antiandrogen therapy, four had been previously treated with ADT, and three had never received ADT or antiandrogens. Men who presented on ADT or antiandrogen therapy were encouraged to undergo a trial of these medications before beginning TTh. Three did so, and returned after minimum of 3 months still requesting initiation of TTh. Median duration of TTh was 9.5 months (IQR 7–24). Median PSA doubling time (IQR) was 4.4 months (2.4–8.3).

Eight men were treated with at least one cycle of mBAT and six received continuous TTh through injections, gels, or subcutaneous pellets.

Follow-up imaging was available for 10 men at 3–12 months after initiating TTh. Seven showed no progression and three showed progression, all with new foci of bone metastases.

Three men died during TTh: one from PCa at 95 years from PCa after 10 months TTh; one at 73 years from myelofibrosis, 7 years after beginning TTh; and one at 75 years after 10 months TTh from peptic ulcer disease. One additional man died of PCa, 2 years after discontinuing TTh. Complications during TTh included myocardial infarction (MI) at 6 months in a patient with three prior strokes, the most recent being 2 years before initiation of TTh; bone marrow replacement by PCa 3.5 years after first development of bone metastases; urinary retention with urosepsis 3 months after initiation of TTh; and a recurrent deep vein thrombosis 8 months after beginning TTh. There were no cases of pulmonary emboli, pathological fractures, or acute spinal cord compression. Of the 11 men still alive, 2 discontinued TTh due to PCa progression, 4 discontinued TTh on the recommendation of their local physicians, and 5 continued treatment with TTh. Overall mortality in this group was 21.4% and PCS mortality was 7.1%. Median baseline and final PSA values for BCR and MET groups are shown in Figure 1.

Adjuvant ADT

Two men with Gleason 8 PCa initially treated with ADT for high-risk disease after stereotactic radiation therapy treatment received TTh for a median of 14 months (12–16). One was treated for 9 months with combination leuprolide and enzalutamide, and developed impaired cognition, unusually slow speech and movements. Leuprolide was discontinued together with initiation of TTh, while continuing enzalutamide. The second patient was treated with leuprolide for 1 year, then discontinued due to disabling fatigue, and began TTh 5 months later. Mean testosterone levels increased from 50 to 854 ng/dL. Mean PSA increased from 0.01 to 0.3 ng/mL while on TTh. No adverse events were noted. The second patient discontinued TTh at 1 year at urging of his local

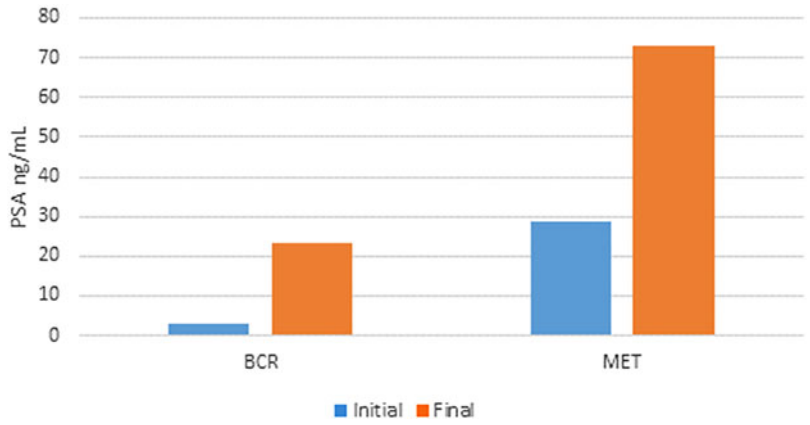

FIG. 1. Median changes in prostate-specific antigen with testosterone therapy.

physician, and the first continues with TTh in combination with enzalutamide with greatly improved cognition and ease of movement.

Discussion

To the best of our knowledge this is the first reported clinical series in the PSA era of outcomes with TTh specifically in men with BCR or MET in a clinical setting, and not part of a formal trial. A total of 20 men with nonlocalized PCa and two receiving ADT deemed at high risk for metastases received TTh for up to 7 years with a median duration of >1 year, with considerable subjective improvement in quality of life, and without rapid progression, morbidity, or death. There was only one PCa-specific death during TTh, occurring 11 months after initiation of TTh in a 94-year-old man with diffuse metastases and initial PSA 546 ng/dL. Although this series of cases cannot establish safety of TTh in the setting of advanced PCa, these results do challenge the long-standing assumption that even transient exposure to increased serum T in a man with advanced PCa-with testosterone flare, for example, will rapidly precipitate morbidity or death.[15]

The original basis for the belief that TTh is dangerous for PCa arose from the work of Huggins and Hodges, who in 1941 concluded that "Testosterone injections cause activation of prostate cancer[1]" Contemporary review of their original data revealed it was based on erratic acid phosphatase data for only 14 days in a single hormonally intact individual.[16] Fowler and Whitmore reported 45 of 52 men who received TTh demonstrated an undefined "unfavorable result" within 30 days; however, all but four of these men had already undergone castration or were on estrogen treatment to suppress serum T.[2] Of these four men, three demonstrated no unfavorable results despite daily injections of T propionate for 51, 55, and 310 days. The appearance of poor outcomes for men on ADT but not for men who were hormonally intact inspired the development of the saturation model, which demonstrates a finite capacity of androgens to stimulate PCa growth, with exquisite sensitivity to changes in androgen concentrations at low values, and then insensitivity once the saturation point is reached,[9] which appears to be ~250 ng/dL in men.[17,18] This study provides suggestive evidence for saturation in nonlocalized PCa, since men with BCR failed to demonstrate precipitous increases in PSA despite substantial periods of TTh.

There is scant literature regarding testosterone administration in men with advanced PCa in the PSA era. Leibowitz et al. reported results of a variety of strategies involving TTh in a mixed population of 96 men with PCa, of which it appears 31 likely had metastatic disease.[19] Clinical trials of BAT in men with castrate-resistant prostate cancer reported a PSA decline in 7 of 14 men, and evaluable disease was reduced in 5 of 10 men.[12] To optimize the duration of time on TTh, mBAT was developed[13] and was used in seven men in the MET group in this study.

There are several notable observations from this clinical series. First, there exists a set of men for whom quality of life is more important than duration of life. Each patient understood that their choice of TTh could cause immediate or hastened disease progression, morbidity, and death. Second, these men only continued TTh because it provided them with

symptomatic benefits to a degree that made it worthwhile, in their estimation, to risk their lives. This defies a frequently made assertion that TTh provides only minimal symptomatic benefits.[20] Nearly all men experienced increased vigor. Sexual desire and ability were improved in many, and several were able to resume sexual activity after years without it, especially those on ADT. One man gained enough strength to give up the need for a walker. Several men and their partners noted a return of their "personality." One regained fluency of speech and brain processing that had been severely compromised by ADT. Further research in this area would benefit from use of validated instruments to address subjective response to treatment.

Arguably the most important observation from this study is that TTh was not associated with rapid disease progression. Among men with BCR, with median duration of 33 months of TTh, only one progressed to metastatic disease >5 years after beginning TTh. This compares with 3 years estimates of metastatic disease in men with BCR after RP of 14% for Gleason score 5–7 and 37% for Gleason score 8–10.[21] Hruby et al. reported that 70 of 538 men demonstrated biochemical failure after XRT for localized PCa with median follow-up of 50 months. Of these 70 men with biochemical failure, 13 had died and metastases were observed in 5 of the remaining 57 (8.8%).[22] Only 30% of men with MET demonstrated progression on follow-up imaging studies by 3–12 months. The overall survival of 79.6% (mortality 21.4%) in the MET group compares with median survival of 47.2 months in the ADT alone arm of the CHAARTED Trial.[23] The relevance of the short median PSA doubling times of 8.9 months in BCR and 4.4 months in MET is uncertain, as PSA doubling times are not usually determined in men receiving androgens, particularly since PSA expression is itself androgen-dependent.[24]

There are several important limitations to this study, including its retrospective nature, multiple forms of TTh treatment, and small sample size. In addition, PCa is a heterogenous disease, and this report includes those with Gleason scores ranging from 6 to 9, which may cloud interpretation of results. Nonetheless, these preliminary results indicate that TTh does not appear to cause precipitous PCa progression in men with BCR and MET. There may be a role for TTh in selected men with BCR, MET, or high-risk disease willing to accept the theoretical risk of hastened disease progression in return for enhanced quality of life.

Conclusion

TTh in men with BCR, MET, and high-risk PCa was associated with symptomatic benefits and low rates of complications, although interpretation of these results must be tempered by small sample size and a heterogeneous population. Well-designed prospective studies are needed to provide better evidence for the potential use of TTh in similarly affected individuals. In the meantime, these results may provide clinicians with a framework to counsel patients who prioritize quality of life over longevity.

Authors' Contributions

Data extraction by A.M.; data analysis and drafting of the article by A.A. and A.M.; critical revision of article for important intellectual content by A.A., G.B., and A.M.

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Abbreviations Used

ADT = androgen deprivation therapy
BAT = bipolar androgen therapy
BCR = biochemical recurrence
HIFU = high-intensity focused ultrasound
IQR = interquartile range
mBAT = modified BAT protocol
MET = metastatic PCa
PCa = prostate cancer
PCS = prostate cancer-specific
PSA = prostate-specific antigen
RP = radical prostatectomy
T = testosterone
TTh = testosterone therapy
XRT = external beam radiotherapy