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Original Article

Reversing the effects of androgen-deprivation therapy in men with metastatic castration-resistant prostate cancer

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Objective

To investigate whether bipolar androgen therapy (BAT), involving rapid cyclic administration of high-dose testosterone, as a novel treatment for metastatic castration-resistant prostate cancer (mCRPC) promotes improvements in body composition and associated improvements in lipid profiles and quality of life.

Patients and Methods

Men from two completed trials with computed tomography imaging at baseline and after three cycles of BAT were included. Cross-sectional areas of psoas muscle, visceral and subcutaneous fat were measured at the L3 vertebral level. Functional Assessment of Chronic Illness Therapy – Fatigue questionnaire and 36-item short-form health survey were used to assess quality of life.

Results

The 60 included patients lost a mean (SD) of 7.8 (8.2)% of subcutaneous fat, 9.8 (18.2)% of visceral fat, and gained 12.2 (6.7)% muscle mass. Changes in subcutaneous and visceral fat were positively correlated with each other (Spearman's correlation coefficient 0.58, 95% confidence interval 0.35–0.71) independent of the effects of age, body mass index, and duration of androgen-deprivation therapy. Energy, physical function, and measures of limitations due to physical health were all significantly improved at 3 months. The improvements in body composition were not correlated with decreases in lipid levels or observed improvements in quality of life.

Conclusions

In the present study, BAT was associated with significant improvements in body composition, lipid parameters, and quality of life. This has promising implications for the long-term health of men with mCRPC.

Keywords

prostate cancer, body composition, androgen-deprivation therapy, cancer survivorship, metastatic castration-resistant prostate cancer, bipolar androgen therapy, #PCSM, #ProstateCancer, #uroonc

Introduction

The primary treatment for metastatic prostate cancer is androgen-deprivation therapy (ADT), which is continued indefinitely once started [1]. The low testosterone state induced by ADT has negative impacts on body composition, causing an increase in body fat, a decrease in muscle mass, and alteration of lipid profiles [2–4]. ADT has been associated with a loss of ~5% of muscle mass and a gain of up to 10% of body fat, including both subcutaneous and visceral fat [2–4]. Furthermore, it has been associated with increases in total cholesterol, low- and

high-density lipoprotein (LDL and HDL) levels, as well as triglyceride (TG) levels [5]. These changes are relevant because cardiovascular disease (CVD) is a major cause of morbidity and mortality in men with prostate cancer and these alterations in CVD risk factors may contribute to the possible link between CVD and ADT [6,7]. Furthermore, low muscle mass, i.e. sarcopenia, and high levels of subcutaneous fat both associated with ADT, have been associated with poor outcomes in metastatic castration-resistant prostate cancer (mCRPC), including lower overall survival among men with advanced prostate cancer [8–10].

Newer oral therapies in prostate cancer targeting the androgen axis such as abiraterone, a cytochrome P450 17A (CYP17A) inhibitor, and enzalutamide, an androgen receptor antagonist, have improved overall survival for men with mCRPC [11,12]. However, the addition of these agents to ADT is further associated with negative effects on body composition such as skeletal muscle loss and body fat increases, which may contribute to the increased risk of CVD in these patients [8,13–15].

Bipolar androgen therapy (BAT) is the cyclic administration of high-dose testosterone in men who remain on long-term LHRH agonists or antagonists [16]. The effect of this therapy is rapid cycling between the polar extremes of supraphysiological and near-castrate serum levels of testosterone [16]. This strategy has been associated with tumour responses in men with mCRPC [17,18]. We hypothesised that this rapid cycling would also promote improvements in body composition, lipid profiles, and quality of life that would be a counter to the effects of anti-androgen therapies.

Patients and methods

Patients

Data were pooled from two completed clinical trials at a single institution: TRANSFORMER (NCT02286921) and RESTORE (NCT02090114). The TRANSFORMER trial was a randomised trial in men with progressive mCRPC after treatment with abiraterone who received either BAT or enzalutamide, with the option for cross-over after progression [19]. Men treated with BAT on trial were screened for eligibility. In both trials, 400 mg testosterone cypionate was given intramuscularly and LHRH agonists were continued. The RESTORE trial was a single-arm trial of men who had progressive disease after either abiraterone or enzalutamide and who then were treated with BAT [17,20]. Patients who received BAT therapy prior to enrolment ($n = 11$), who were not previously treated with abiraterone or enzalutamide ($n = 24$), or did not have CT imaging performed within the Johns Hopkins medical system ($n = 10$) were excluded. Participants in both protocols had CT imaging at baseline (just prior to start of BAT) and after three 28-day cycles of BAT.

Anthropometry based on CT Image Analyses

The CT scans taken at baseline and 3 months were analysed by three readers of varying training levels: attending radiologist (R.G.), 2 years postgraduate level (J.T.) and second year medical student (V.D.). All readers were blinded to patient identity, characteristics, and study group, and to the measurements made by the other readers. OsiriX v10.0.4 (Pixmeo Sàrl, Bernex, Switzerland) software was utilised to perform the image analysis. A slice at the L3 vertebral level, determined by the attending radiologist, was used by all readers to make measurements, consistent with previous studies and because analyses here are associated with estimates of whole body composition measurements [21]. Readers first generated a closed polygon between the visceral adipose layer and abdominal muscle layer and then generated regions of interest (ROIs) using attenuation values for the various tissue types (muscle: −30 to 150 Hounsfield units [HU], subcutaneous adipose tissue: −190 to −30 HU, and visceral adipose tissue: −150 to −50 HU) [22]. The psoas muscle was individually segmented using a closed polygon around the bilateral psoas. Cross-sectional areas (cm^2) of psoas muscle, visceral adipose tissue, and subcutaneous adipose tissue were measured using the newly created ROIs. Inter-reader variability was calculated and the measurements obtained by the three readers were averaged.

Measures

Lipid panels were obtained as part of the trial protocol at start of testosterone and at 3 months after BAT treatment. Optimal lipid parameters were defined based on the National Cholesterol Education Program/Adult Treatment Panel III Guidelines [23]. This categorises the thresholds for optimal LDL levels as <100 mg/dL, HDL levels >60 mg/dL, and TG levels <150 mg/dL. HDL levels <40 mg/dL are considered low. Sarcopenia was defined as having a Skeletal Muscle Index (SMI), based on the area of the psoas muscle at L3, divided by the height in meters (cm^2/m^2) of <55 cm^2/m^2, which is consistent with consensus definitions on cachexia in patients with cancer [24]. The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale and the 36-item short-form health survey (SF-36) questionnaires were used to measure fatigue, energy, physical functioning levels, emotional well-being and limitations due to physical health at baseline and at 3 months [25–27].

Statistical Analysis

Patient characteristics were summarised via descriptive statistics (mean/SD or median/range for continuous variables, and frequency/percentage for categorical variables). Consistencies of body composition measures from three different readers at each time point were first assessed via intraclass correlation coefficients (ICCs). As a result of the high yield ICC (>0.96), the mean value of body composition measures among the three readers was utilised for each individual patient at each time point. Changes in body composition were summarised by the percentage change from baseline as a way of individual normalisation. The means of the baseline and 3-month values for the outcomes were reported and the distributions of differences, from baseline to 3 months, were tested via paired Wilcoxon tests. Associations

between changes of body composition measures, and the associations between body composition changes and lipid level changes or changes of quality-of-life outcomes were assessed via Spearman's correlation coefficients. In addition, linear regression models were used for testing the associations between changes of outcomes (changes of body composition outcomes, changes of lipid outcomes, and changes of quality-of-life outcomes) and patient characteristics (pre-specified for patient age at baseline, body mass index [BMI], and duration of prior ADT). The associations between changes of body composition measures and changes of lipid outcomes with adjustment of patient characteristics were examined via multivariable linear regression models. The McNemar test was used for assessing the differences in the percentage of sarcopenic patients before and after treatment. Statistical analyses were conducted using R, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). All *P* values were calculated using two-sided tests with a threshold of 0.05 significance level.

Results

A total of 60 patients were included in the final cohort. Baseline patient characteristics are shown in Table 1. The median age of the cohort was 73 years and 85% of the patients were White. Two-thirds of the population had localised disease at initial diagnosis, while one-third had *de novo* metastatic disease. Additionally, 30% had Gleason Grade ≤7, 27% had Gleason 8 disease and 43% had Gleason 9 or 10 disease. The mean (SD) time on ADT was 4 (5.7) years. All patients had received prior abiraterone or enzalutamide and only three patients (5%) had received any prior chemotherapy. The mean (SD) BMI at baseline was 29.3 (4.6) kg/m^2, with 17% classified as having a normal BMI, 43% as overweight and 40% as obese. Bone metastases were the most common site of metastatic disease (48 patients, 80%), followed by lymph node metastases (23, 38%) and visceral disease (three, 5%), with 13 patients having more than one site of disease (22%). The median (interquartile range) baseline PSA was 28.6 (9.6–68.2) ng/mL and 27 of the patients had PSA responses (45%) during these 3 months. There was excellent interclass concordance between the readers for each of the measures of body composition (Table 2 with all ICCs >0.96).

Body Composition

The patients lost a mean (SD) of 7.8 (8.2)% of subcutaneous fat and 9.8 (18.2)% of visceral fat, with 83% of patients having at least some loss of subcutaneous fat and 68% of patients with some visceral fat loss (Fig. 1A). The mean subcutaneous fat area was 265 cm^2 at baseline, which decreased to 245 cm^2 at follow up (*P* value for difference < 0.01). Mean visceral fat decreased from 233 to 213 cm^2

Table 1 Baseline characteristics of patients with mCRPC who were treated with at least 3 months of BAT as second-line and later therapy on RESTORE (*n* = 45) or TRANSFORMER (*n* = 15) (cohorts A/B).

Variable	Value
Age at start of BAT, years, median (range)	73, (50–87)
Race, *n* (%)	
White	51 (85)
Black	5 (8)
Other	4 (7)
Stage at diagnosis of prostate cancer	
Localised	40 (67)
metastatic	20 (33)
Gleason score	
6	2 (3)
7	16 (27)
8	16 (27)
9–10	26 (43)
Duration of prior ADT, years, mean (SD)	4 (5.7)
Year of BAT treatment, *n* (%)	
2014–2016	44 (73)
2017–2018	16 (27)
Sites of metastatic disease, *n* (%)	
Any bone metastases	48 (80)
Any lymph node metastasis	23 (38)
Visceral	3 (5)
Prior chemotherapy, *n* (%)	3 (5)
Prior abiraterone or enzalutamide, *n* (%)	60 (100)
BMI at baseline (start of BAT), kg/m^2, mean (SD)	29.3 (4.6)
BMI (kg/m^2) category at baseline (start of BAT), *n* (%)	
<25	10 (17)
25–30	26 (43)
≥30	24 (40)
PSA level, ng/mL	
Baseline PSA, mean (SD)	51 (67)
Baseline PSA, median (interquartile range)	29 (10–68)
PSA responses, *n* (%)	
Any response (decline in PSA from baseline)	27 (45)
No response	33 (55)
Bone protective agents, *n* (%)	
Yes	29 (48)
No	31 (52)

Table 2 Concordance between readers in outcomes of subcutaneous (SQ) fat, visceral (VC) fat, and muscle mass.

Outcomes	N	ICC
Baseline		
Subcutaneous fat	19	0.998
Visceral fat	19	0.999
Muscle mass	20	0.963
3-month follow up		
Subcutaneous fat	17	0.998
Visceral fat	17	0.999
Muscle mass	17	0.991

(*P* value for difference < 0.01). Neither baseline age at start of BAT treatment nor baseline BMI influenced the degree of change of body composition measures (all *P* > 0.05). The duration of prior ADT did not impact the degree of subcutaneous or visceral fat lost (*P* = 0.51 and *P* = 0.07). Changes observed in subcutaneous fat were positively

Fig. 1 Overview of measurements at baseline and at 3-month follow-up after BAT for (**A**) body composition outcomes: subcutaneous (SC) fat, visceral (VC) fat, and muscle mass (MM); (**B**) lipid outcomes: LDL, HDL and TGs; (**C**) quality-of-life outcomes: FACIT-Fatigue scale (Facit), Energy, Physical Functioning (Phys), Emotional well-being (Emot), and Limitations due to physical health (Limits). Red lines indicated the corresponding mean values. Measurements from the same individual were connected with grey lines.
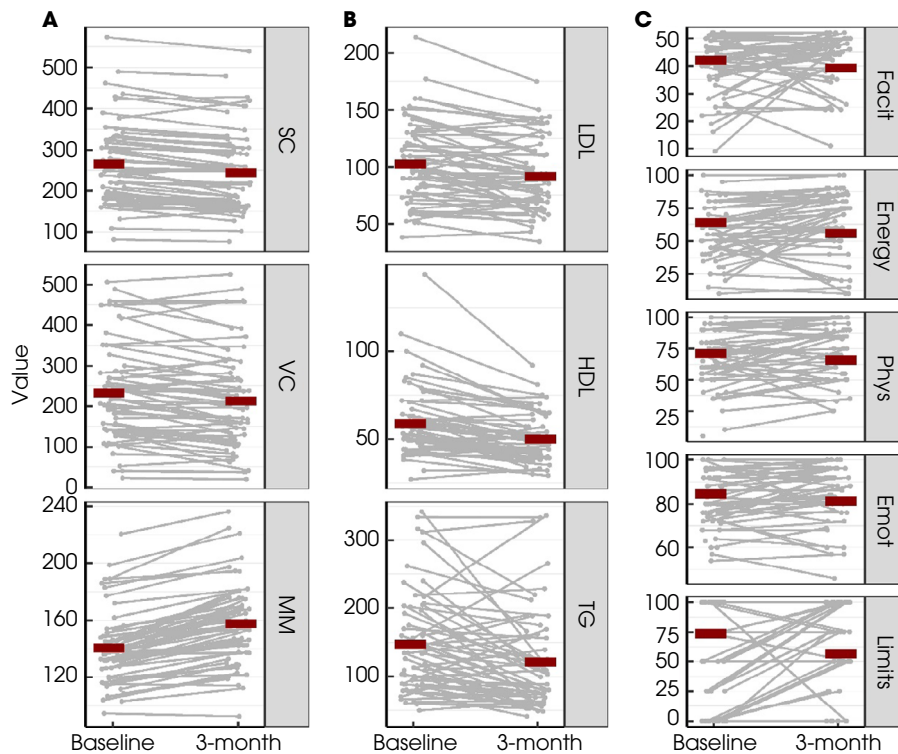
correlated with the changes in visceral fat (Spearman's correlation coefficient 0.58, 95% CI 0.35–0.71) and this was independent of effects of age, BMI, and duration of ADT.

The patients gained a mean (SD) of 12.2 (6.7)% muscle mass in 3 months, with 97% of patients having some gain of muscle mass. Figure 2 shows a representative analysis of the increase in muscle mass seen with 3 months of BAT treatment. The mean muscle area increased from 140 to 158 cm^2 (*P* value for difference < 0.001). The duration of ADT did have a significant impact on the degree of muscle mass gained (*P* = 0.02). Patients who had a prior duration of ADT of <4 years gained a mean (SD) of 9.7 (6.1)% muscle mass compared to a 14.7 (6.4)% gain of muscle mass among men who were on ADT for ≥4 years (*P* for difference = 0.003). A summary of the changes is shown in Table 3. In total, 55 (92%) patients were sarcopenic at baseline and the proportion of sarcopenia was significantly lower (75%, *P* = 0.004 for difference between baseline and follow-up) at the 3-month follow-up after BAT treatment.

Lipids

The LDL levels decreased significantly by a mean (SD) of 12.4 (19.1) mg/dL, with 74% of patients having a decrease in LDL levels (*P* for difference < 0.001; Fig. 1B). Among the 32 patients who had baseline LDL levels above the optimal level (≥100 mg/dL), 14 (44%) had LDL levels at follow-up that were <100 mg/dL and in the optimal range.

The HDL levels decreased by a mean (SD) of 9.1 (11.4) mg/dL (*P* for difference < 0.001; Table 3) and 16% of patients had an increase in their HDL levels (Fig. 1B). There were only three patients who had HDL levels of <40 mg/dL at baseline, which would be considered low. None of these three patients had follow-up levels that were >40 mg/dL at 3 months.

The TG levels significantly decreased by a mean (SD) of 26.9 (59.2) mg/dL (*P* for difference = 0.005; Table 3) with 69% of patients having some decrease in TG levels (Fig. 1B). Of the 23 patients who had TG levels of >150 mg/dL at baseline, 48% were within goal range, <150 mg/dL, at follow-up.

No associations were observed between changes of lipid measures and patient characteristics (baseline age at start of BAT treatment, baseline BMI and duration of ADT; all *P* > 0.05). Associations between changes in visceral fat and LDL or TG levels did not approach statistical significance (*P* = 0.09 and *P* = 0.92, respectively). Similarly, there was no

Fig. 2 Image of CT abdomen at L3 vertebral level with segmentation of visceral fat (yellow area), subcutaneous fat (blue area) and abdominal wall musculature (red area) performed manually with OsiriX at 3-month interval between the two scans (**A,B**).
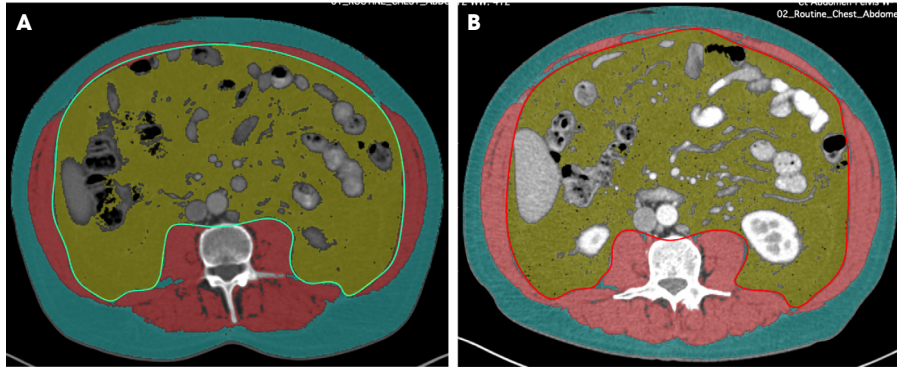
Table 3 Summary Statistics for body composition measures and lipid parameters at baseline and at 3-month follow-up after initiation of BAT.

	Baseline, mean (SD)	3-month follow-up, mean (SD)	% of ↑/↓ from baseline to 3-month follow-up	% change from baseline to 3-month follow-up, mean (SD)	*P* value for difference*
Subcutaneous fat area, cm^2	265.1 (98.3)	245.0 (96.0)	83 ↓	↓ 7.8 (8.2)	<0.001
Visceral fat area, cm^2	233.1 (119.1)	212.5 (121.8)	68 ↓	↓ 9.8 (18.2)	0.001
Muscle area, cm^2	140.4 (24.4))	157.5 (27.8)	97 ↑	↑ 12.2 (6.7)	<0.001
LDL, mg/dL	102.4 (35.5)	91.6 (31.2)	74 ↓	↓ 12.4 (19.1)	<0.001
HDL, mg/dL	59.0 (20.1)	49.7 (13.5)	84 ↓	↓ 9.1 (11.4)	<0.001
TGs, mg/dL	146.9 (73.8)	121.3 (71.9)	69 ↓	↓ 26.9 (59.2)	0.0005
FACIT-F scale	39.3 (10.5)	42 (9.6)	52 ↑	↑ 2.11 (12.6)	0.33
Energy	56.1 (21.1)	64.1 (24.7)	63 ↑	↑ 7.8 (19.5)	0.004
Physical functioning	66.0 (22.3)	70.9 (21.8)	54 ↑	↑ 4.2 (15.5)	0.05
Emotional well being	81.2 (12.3)	84.4 (13.2)	54 ↑	↑ 1.8 (8.6)	0.09
Limitations due to physical health	56.5 (43.7)	73.4 (36.3)	38 ↑	↑ 13.9 (32.2)	<0.001

**P* values were testing the differences of outcome's distribution between baseline and 3-month follow-up after BAT therapy via Wilcoxon signed-rank test.

significant association between changes in muscle mass and changes in HDL ($P = 0.61$).

Quality of Life

Energy levels and physical functioning levels significantly improved from baseline to 3 months ($P = 0.004$ and $P = 0.05$ for change, respectively), as did limitations due to physical health ($P < 0.01$) (Table 3, Fig. 1C). However, none of these improvements were correlated with a change in muscle mass, visceral body fat, or subcutaneous body fat. There was no significant change in the absolute change from baseline to 3 months on fatigue (measured by FACIT-F; $P = 0.33$) or emotional well-being ($P = 0.09$; Table 3). While most patients reported improvements in energy, physical functioning, and emotional well-being, 46% (95% CI 31–61), 39% (95% CI 25–55), 28% (95% CI 16–43) of patients respectively, reported improvements that would be considered clinically meaningful [28]. On average, the changes seen in limitations due to physical health are considered clinically meaningful [28]. No

statistically significant associations were observed between changes in quality of life and patient characteristics (baseline age at start of BAT treatment, baseline BMI and duration of ADT; all $P > 0.05$).

Discussion

The present study demonstrates that three cycles of BAT therapy in patients with mCRPC is associated with significant positive changes in body composition, lipid profiles, and measures of quality of life. Subcutaneous and visceral fat decreased by 7.8% and 9.8% respectively, while muscle mass increased by 12.2% on average. Additionally, LDL, HDL and TG levels decreased with BAT therapy by 12.4, 9.1, and 26.9 mg/dL, respectively. In studies with BAT performed to date, the duration of BAT has ranged from 1 to 60 months. Longer-term treatment with BAT may produce an even greater effect on body composition, although this must be confirmed in larger studies. While there did not seem to be a significant difference in the rate of cardiovascular thrombotic

events in the context of the clinical trials, the long-term effect on cardiovascular health given these changes will need to be studied.

Although patients were analysed after only 3 months of BAT, these findings are consistent with data from previous studies of BAT in men with metastatic hormone-sensitive prostate cancer, where there was an improvement in quality-of-life scores [29]. It is also consistent with findings on supplementation of testosterone in the non-cancer patient population. In a meta-analysis of testosterone supplementation, it was found that testosterone was associated with a decrease in fat and an increase in muscle mass [30]. Among men who were hypogonadal at baseline, there was also an improvement seen in lipid profiles with decreases in total cholesterol and TGs [30]. There have been varying results of testosterone supplementation on older men in the literature. In one study of 24 men with a mean (SD) age of 57.5 (4.8) years with type 2 diabetes and visceral obesity, oral testosterone supplementation decreased visceral fat by 5.7% after 3 months [31]. Another study of men aged 65–85 years did not show changes in body composition with testosterone supplementation after 12 weeks; however, the doses used in the study (testosterone patch that delivered 5 mg testosterone over 24 h) were lower than used in other studies and in our present study. Testosterone supplementation in hypogonadal men has been associated with small decreases in cholesterol, up to 5 mg/dL, with no significant changes in TGs [32]. In older obese men (aged 62–78 years), testosterone supplementation was associated with a significant decrease in LDL (13.5 mg/dL), HDL (5.4 mg/dL) and TGs (35 mg/dL), consistent with our present study [33]. Meta-analyses of randomised studies on the effect of testosterone supplementation in hypogonadal men do show consistent improvements in quality of life, in particular energy levels, consistent with our present study [34].

There are no other therapies for prostate cancer that have produced such results in terms of body composition and lipid profiles, although some, including bone protective agents, may improve quality of life [35]. Exercise, both resistance and aerobic training, have had varying success in improving body composition parameters with estimates of up to 16% increase in muscle mass and as much as 29% loss of body fat, although the results are quite variable [36]. Pooled analyses have not shown a benefit of exercise on lipid profiles in men with prostate cancer treated with ADT [37,38].

Conclusion

BAT, a novel treatment strategy being studied for mCRPC, is associated with significant improvements in body composition, lipid parameters, and a decrease in the proportion of sarcopenic patients after 3 months of treatment. This is the only therapy to date for the treatment of advanced prostate cancer that is associated with these improvements and has promising implications for the long-term health of men with mCRPC.

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Disclosure of Interests

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Author Contributions

Catherine H. Marshall: drafted, revised manuscript; data collection and analysis and design, interpretation of results. Jessa Tunacao, Varun Danda, Rakhee Gawande, Clifford R. Weiss: data acquisition and interpretation; revised manuscript. Hua-Ling Tsai, John Barber: statistical design and analysis. Samuel R. Denmeade, Corinne Joshu: conceived/ designed work, collected data, interpretation of results, and revision of manuscript.

Ethics Approval and Consent to Participate

All participants signed informed consent to participate in the clinical trials. The study was performed in accordance with the Declaration of Helsinki.

Consent for Publication

Not applicable.

Data Availability Statement

Data are from a clinical trial and individual patient data are not available publicly.

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Abbreviations: ADT, androgen-deprivation therapy; BAT, bipolar androgen therapy; BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; HU, Hounsfield units; ICC, intraclass correlation coefficient; LDL, low-density lipoprotein; mCRPC, metastatic castration-resistant prostate cancer; ROI, region of interest; TG, triglyceride.