



Published in final edited form as:

Prostate Cancer Prostatic Dis. 2021 September ; 24(3): 725–732. doi:10.1038/s41391-020-00317-w.

BODY COMPOSITION, PHYSICAL FUNCTION AND QUALITY OF LIFE IN HEALTHY MEN AND ACROSS DIFFERENT STAGES OF PROSTATE CANCER

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Abstract

BACKGROUND: Androgen deprivation therapy (ADT) for prostate cancer (PC) has detrimental effects on physical function and quality of life (QoL), but the addition of androgen receptor signaling inhibitors (ARSI) on these outcomes is unclear.

PURPOSE: To compare body composition, physical function, and QoL across progressive stages of PC and non-cancer controls (CON).

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Conflict of Interest

The authors have no conflicts of interest to report.

METHODS: In men with hormone sensitive PC (HSPC, n=43) or metastatic castration-resistant PC (mCRPC, n=22) or CON (n=37), relative and absolute lean and fat mass, physical function (6m walk, chair stands, timed up and go [TUG], stair climb), and QoL were determined.

RESULTS: Relative body composition differed amongst all groups, along with ~39% greater absolute fat mass in mCRPC vs. CON. TUG and chair stands were ~71% and ~33% slower in mCRPC compared to both CON and HSPC, whereas stair climb was ~29% and 6m walk was ~18% slower in mCRPC vs. CON. Relative body composition was correlated with physical function ($r=0.259-0.385$). Clinically relevant differences for mCRPC were observed for overall QoL and several subscales vs. CON, although body composition and physical function did not influence QoL.

CONCLUSIONS: PC progression is associated with deteriorations in body composition and physical function. As ADT length was similar between groups, ARSI use for mCRPC likely contributed in part to these changes. Given the difficulties of improving lean mass during ADT, interventions that reduce adiposity may lessen the side effects of hormone therapy.

Keywords

androgen deprivation therapy; exercise oncology; activities of daily living; advanced prostate cancer

INTRODUCTION

Prostate cancer (PC) accounts for ~200 000 new cases annually in the United States alone, making it the most common non-dermatological tumor in men (1). Androgen deprivation therapy (ADT) reduces testosterone levels and slows tumor progression (2) but has adverse effects, including decreased lean and bone mass, increased fat mass (3–7) and reduced physical function (5, 8–11) and quality of life (QoL) (12–14). However, the effect of ADT in men with more advanced PC is not clearly defined.

With time, PC may progress to castration resistance (15) and metastasize to sites such as lymph nodes or bone (16), claiming the lives of ~33 000 men per year (1). Metastatic castration-resistant prostate cancer (mCRPC) often requires the addition of secondary hormonal therapies (17). Although abiraterone acetate and enzalutamide affect the androgen axis via different mechanisms, these androgen receptor signaling inhibitors (ARSI) delay tumor progression and improve survival outcomes (18, 19). However, there are additional side effects to be considered. Relative to a 1.2% decrease in lean mass from ADT (7), abiraterone reduced lean mass by 4.3% over ~6 mo while also increasing fat mass (20). Fall risk, hypertension and fatigue also increase with enzalutamide (18, 21, 22). While increased falls and fatigue are suggestive of poorer physical function, direct measures are lacking during mCRPC treatment. Moreover, ARSI may affect QoL in different ways. For example, among older men (>75y), QoL scores increased over 24 weeks with abiraterone while enzalutamide use resulted in greater proportions of men having clinically significant declines in functional and physical well-being (23). While QoL degradation occurred over time in both groups, scores were higher with lower self-reported pain when combining abiraterone with ADT vs. ADT alone (12).

With a lack of direct measures of body composition, physical function and QoL and few comparisons to men with less advanced PC, the true estimates of decline with mCRPC are poorly defined. As such, designing effective interventions is challenging as exercise oncology guidelines are generally written for localized disease (24, 25), primarily due to insufficient evidence in metastatic PC. However, metastatic PC has the highest 5y survival rates of the major cancer types (1) and ARSI increases overall survival (18, 19). Accordingly, this population may benefit greatly from therapies that target physical function and QoL. Consequently, the primary purpose of this study was to estimate differences in body composition, physical function, and QoL across progressive stages of PC and compared to non-cancer controls (CON). We also sought to determine if associations exist between body composition, physical function, and QoL. We hypothesized that ARSI use for mCRPC would exacerbate changes in body composition, physical function, and QoL vs. ADT alone and that increased fat mass and decreased lean mass would be associated with lower physical function and QoL.

METHODS

Design

This cross-sectional analysis included data from 4 previously published cohorts that assessed body composition, physical function, and QoL in prospective clinical trials or case-control studies (26–29). Men were recruited via local advertisements, PC support groups, and from referrals by physician collaborators.

Participants

Men with hormone sensitive PC (HSPC; n=42) were sedentary (no regular exercise except walking over past 6 mo) and were screened for conditions that would contraindicate exercise, including symptomatic cardiovascular or respiratory diseases, pain with exertion, Type 1 diabetes, history of bone fractures, or lack of medical clearance from their physician and included men on continuous ADT (n=28) in the form of luteinizing hormone releasing hormone agonists or anti-androgens for at least 3 mo with total testosterone levels <50ng/dL (26, 27, 29). The mCRPC cohort (n=22) met the same criteria as HSPC, were not currently on chemotherapy, and most were receiving ARSI treatments. Non-cancer controls (CON; n=37) met all inclusion criteria but had no PC history (28). All participants completed detailed medical histories questionnaires and provided written informed consent. Ethics committees at the University of Maryland, College Park, Peter MacCallum Cancer Centre, Victoria University, Western Health, and the University of North Carolina approved this project. The study was performed in accordance with the Declaration of Helsinki.

Body Composition

Body composition was assessed using whole-body dual-energy x-ray absorptiometry (Discovery W, model QDR 4500A Hologic, Waltham, MA, USA) to determine absolute and relative total fat and lean mass. All scans were performed and analyzed by the same certified densitometrist and the machine was calibrated daily.

Functional Tasks

All physical function tasks were explained, demonstrated, and participants performed a practice repetition. Two attempts were made (unless noted otherwise) with the fastest trial recorded.

6m-Rapid Walk.—Maximal walking speed was assessed by the time required to cover 6m as described previously (27, 28).

5 Chair Stands.—Using a straight-backed, armless chair (43 cm), participants fully stood without the use of their arms before returning to a seated position for a total of five repetitions (28). A subset of HSPC (n=19) completed as many chair stands as possible in 30s (27). Values were converted into the time per chair stand and multiplied by five to provide a comparable value. Only one set of chair stands were performed.

Timed-Up-&-Go (TUG).—Participants rose from a seated position (43cm chair) and walked around a cone 2.44m away and returned to a seated position.

Stair Climb.—Participants climbed a flight of 9 stairs (19 cm) as quickly as possible, as described previously (27, 28).

QoL Assessment

The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire was used to assess QoL. Clinical meaningful changes were determined as 6–10 points for FACT-P, 5–9 points for Trial Outcome Index (TOI), and 2–3 points for Prostate Cancer Subscale (PCS) (30).

Statistical Analysis

Chi-square and one-way ANOVA was used to compare groups with Tukey Post-Hoc test used to detect any within group differences. Data not meeting normality requirements (Kolmogorov-Smirnov) were log-transformed. Cohen's *d* (*d*) effect sizes were calculated with trivial, small, medium and large effects being defined as <0.2, 0.2, 0.5 and 0.8, respectively. Data are mean (standard deviation) or \pm 95% confidence intervals. Pearson's correlation coefficients were used to assess relationships between all variables. Analyses were performed in SPSS v26 (IBM, Armonk, NY). Statistical significance was $p < 0.05$ (two-sided).

RESULTS

Amongst the physical characteristics, there were trends for age ($p=0.076$) and race ($p=0.058$) differences between groups (Table 1). Prostatectomy and radiation frequency and ADT duration were similar between mCRPC and HSPC.

Body Composition

For absolute fat mass, mCRPC was 39% greater than CON [mean difference (MD)=8.6kg; 95% CI (2.0, 15.1kg); $p=0.007$; $d=0.8$; Fig. 1A]. Percent fat in mCRPC was greater than

HSPC [MD=4.8%; 95% CI (0.4, 9.2%); $p=0.027$; $d=0.7$] and CON [MD=8.3%; 95% CI (3.8, 12.8), $p<0.001$, $d=1.5$], with a trend for HSPC to be greater than CON [MD=3.5%; 95% CI (-0.03, 7.2); $p=0.075$, $d=0.5$; Fig. 1B]. Percent lean was lower in HSPC vs. CON [MD=2.8%, 95% CI (0.05, 5.6.); $p=0.045$, $d=0.6$; Fig. 1B] while mCRPC was lower than both HSPC [MD=4.1%; 95% CI (0.81, 7.3); $p=0.01$, $d=0.7$] and CON [MD=6.9%; 95% CI (3.6, 10.2); $p<0.001$, $d=0.13$].

Functional Tasks

For TUG, mCRPC was 66% slower than CON [MD=4.0s; 95% CI (0.4, 7.6); $p=0.025$; $d=0.6$; Fig. 2A] and 76% slower than HSPC [MD=4.4s; 95% CI (0.3, 8.4); $p=0.031$; $d=0.7$]. mCRPC chair stands were also 37% slower than CON [MD=3.4s; 95% CI (1.0, 5.9); $p=0.004$; $d=1.0$; Fig. 2A] and 29% slower than HSPC [MD=2.8s; 95% CI (0.3, 5.3); $p=0.023$, $d=0.8$]. mCRPC stair climb was 29% slower than CON [MD=1.4s; 95% CI (0.3, 2.4); $p=0.011$; $d=0.7$; Fig. 2B] and 28% slower than HSPC [MD=1.3s; 95% CI (0.1, 2.5); $p=0.03$; $d=0.7$]. mCRPC 6m walk was 18% slower than CON [MD=0.7s; 95% CI (0.01, 1.4); $p=0.048$; $d=0.6$; Fig. 2B] and trended to be 18% slower than HSPC [MD=0.7s; 95% CI (-0.07, 1.5); $p=0.081$; $d=0.7$; Fig. 2B].

Quality of Life

QoL analyses were only available on a subset of CON. Relative to CON, FACT-P was lower in mCRPC [MD=16.9; 95% CI (1.9, 31.9); $p=0.024$; $d=1.2$; Fig. 3A] with a trend for HSPC [MD=12.9; 95% CI (-0.3, 26.0); $p=0.056$; $d=1.0$]. mCRPC also had lower Trial Outcome Index [MD=13.0; 95% CI (1.8, 24.2); $p=0.019$, $d=1.4$] and for Prostate Cancer Subscale [MD=6.5; 95% CI (0.7, 12.3); $p=0.024$, $d=1.0$] vs. CON. HSPC showed trends for lower Trial Outcome Index [MD=8.6; 95% CI (-1.2, 18.4); $p=0.096$; $d=1.0$] and Prostate Cancer Subscale [MD=4.8; 95% CI (-0.3, 9.9); $p=0.07$, $d=1.0$] vs. CON. Large deficits in Physical Well-Being were present in both mCRPC [MD=3.7; 95% CI (0.6, 6.8); $p=0.016$; $d=1.2$; Fig. 3B] and HSPC [MD=2.8; 95% CI (0.07, 5.6); $p=0.044$; $d=1.2$] vs. CON. Large differences in Social Well-Being were seen in HSPC only vs. CON [MD=4.1; 95% CI (0.9, 7.2); $p=0.01$, $d=1.1$].

Correlations

Lower % fat and higher % lean mass were correlated with higher functional capacity (Table 2). Lean mass % was also associated with Trial Outcome Index and a trend for FACT-P ($p=0.069$). Absolute fat mass was correlated with reduced physical function but to a lesser degree. Lean mass showed no relationship with physical function, nor was function associated with QoL.

DISCUSSION

Several key findings arose from this study. For the first time, we report differences in body composition across progressive stages of PC and provide direct assessments of functional deficits during advanced disease. mCRPC had poorer relative body composition, primarily due to greater absolute fat mass. Substantially lower physical function for mCRPC was observed compared to HSPC and CON. QoL was marginally lower in HSPC but large

differences were present in mCRPC. Collectively, these findings provide insight into the potential adverse effects of ARSI for metastatic PC. Interventions to minimize ADT-related side effects should limit gains in adipose tissue, as higher fat mass was associated with lower physical function.

Body Composition

With ~6 mo of ARSI treatment, mCRPC had absolute fat mass that was 8.6kg higher than CON and 3.9kg greater than HSPC, the latter difference having a large effect but was not statistically significant. Increases in fat mass have been well documented in ADT (5–8). In metastatic PC, 3 mo of ADT demonstrated only small increases in total fat mass (0.3–0.7 kg) during usual care (31, 32), although ARSI use was not reported. Using computed tomography, abiraterone decreased visceral and subcutaneous fat (20) while ADT showed no change (33) or even increased visceral fat mass (34). As our DXA measurements did not include visceral fat, we were unable to expand on these conflicting findings.

In contrast to longitudinal studies demonstrating reduced lean mass (3, 6, 7), HSPC and CON had similar levels. One possibility is that HSPC had greater lean mass prior to initiating ADT. As differences in fat mass account for only ~60% of the body mass discrepancy, we suggest that the 2.8% difference (Fig 1B) between groups in relative lean mass argues for this possibility. With abiraterone, abdominal muscle area was decreased by 3–4% after ~6 mo of treatment (20). Somewhat surprisingly, we report only small ($d=0.2$, -1.8%) to moderate ($d=0.5$, -5.3%) non-significant differences in absolute lean mass for mCRPC relative to CON and HSPC, respectively, although % lean mass shows large group differences and are similar to the declines in muscle area reported over time with abiraterone (20).

Physical Function

This is the first report, to our knowledge, to objectively quantify the loss of functionality in mCRPC relative to CON. Both longitudinal and cross-sectional studies show that physical function decreases with ADT (5, 8–11, 35). However, the response may be task specific (36) and appears consistent with the small (non-significant) differences observed between HSPC and CON. For mCRPC, the greatest deficit was in TUG. Due to a lack of comparative data in mCRPC, we compared our data to reference values where older men age 71–75 had a mean TUG time of 8.6 s (37). TUG times for HSPC and CON placed them in the 10th percentile and the lack of group differences was consistent with previous work (35). In contrast, mCRPC was in the 80th percentile and was similar to men age 81–85 years, suggesting mCRPC treatments contribute to ~10 years of age-related functional decline. Furthermore, the deficits in mCRPC vs. HSPC and CON both exceed minimal clinically important differences (35). Slower TUG times is somewhat predictive of falls risk (38) and may contribute to the elevated prevalence of falls with enzalutamide (39). Gait speed is also clinically relevant and while mCRPC gait speed was 20% slower than CON, the 1.3 m/sec we observed exceeds critical thresholds for independent living and mortality (40, 41).

Lower functional performance in mCRPC was greatest in tasks that involved overcoming gravity or change of direction, which may explain why 6m was less affected. As

such, negative alterations in body composition during ADT were hypothesized to impair performance. Indeed, relative lean and fat mass both correlate with physical function to a similar degree, albeit in opposite directions. Absolute fat mass appears to drive this, affecting both relative measures while also being linked to function directly. Surprisingly, absolute lean mass showed no relationship with functional performance but remains consistent with the lack of group differences (i.e. Fig 1A). In older adults, lean mass and strength are often correlated (42) and muscle strength and power are predictive of physical function (43). However, cancer cachexia highlights the disconnect between muscle mass and physical function (44), possibly due to the underlying assumption of a linear relationship. Despite significant hypertrophy following resistance training during ADT, only greater strength was associated with improved physical function (27), implying that neurological adaptations may be more prevalent. While maximal strength was measured in all cohorts, the use of slightly different machines prevented the inclusion of this outcome. Standardized strength assessments should be included in exercise oncology whenever possible (45). When combined with body composition analyses, neurological and lean mass alterations and their respective impact on muscle force and physical function can be teased out to improve exercise prescription during PC treatment.

Quality of Life

QoL was lower in mCRPC for FACT-P, TOI and PCS compared to CON with trends for reductions in HSPC, all of which were large, clinically relevant differences (30). Physical well-being was lower in both PC groups, which is consistent with ADT use for localized PC (13, 14) but also higher fat mass and reduced physical function. As FACT-P is not typically assessed in healthy men, only ~30% of CON completed this task and likely contributed to detecting only trends vs. HSPC. Normative data for FACT-G indicates all groups exceeded the means for healthy men and men with cancer, respectively (46). CON exceeded the mean by a full standard deviation (+17.5 points) while HSPC (+9.7 points) and mPC (+7.3 points) were only ~0.5 standard deviation higher. Irrespective of group, our cohort demonstrated high relative QoL scores that may be the result of the increased functionality and independence required to partake in exercise oncology trials.

In contrast to our hypothesis, the small differences between HSPC and mCRPC were not statistically nor clinically significant. Despite poorer body composition and physical function in mCRPC, neither factor was associated with the reduced QoL and suggests other factors are playing roles. One possibility is bone pain, as the addition of abiraterone vs. ADT alone slowed pain progression, fatigue and deterioration of QoL (12). The physiological and functional deficits and their lack of influence on QoL is attributed to the multi-factorial nature of QoL. We speculate that the ever-present effects of pain have more profound effects on QoL relative to more gradual declines in body composition and physical function that are less noticeable. While type of ARSI influences QoL (23), our abiraterone and enzalutamide samples sizes were too small to be analyzed separately but merit consideration in future studies.

This study had several limitations. The sample size for mCRPC was modest. While the same operator and make/model was used for body composition, data are from different machines.

Compared to HSPC, mCRPC tended to be older, were exposed to more treatments and likely had more comorbidities, and not all mCRPC received ARSI. While tempting to attribute group differences based on ARSI use, these factors could also influence the response.

In summary, PC progression is associated with deteriorations in body composition and poorer physical function. Clinically relevant deficits in QoL are observed in mCRPC and while the differences between HSPC and CON are non-significant, a concerning pattern is present. With recent approval to use ARSIs in hormone-sensitive metastatic PC (47), ARSI-related side effects may now present earlier in the treatment paradigm and potentially lead to greater loss of function and QoL over time. With higher survival rates in mCRPC relative to other advanced cancers, controlling adiposity should help maintain a high standard of living. With ADT attenuating muscle hypertrophy following resistance training (48), findings that extends to metastatic PC (31, 32) and animal models of ADT (49), interventions that increase neurological activation to promote strength gains with have potential to reverse functional declines during PC treatment.

Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

This study was supported by funding from the National Institute of Health grants AG018336, CA127784 and AG000268; the Claude D. Pepper Older Americans Independence Center (P30 AG028747); the Department of Veterans Affairs; Department of Industry, Innovation, and Science of Australia; Research Development grant scheme from Victoria University; the Oded Bar-Or International Scholar Award from the American College of Sports Medicine; and the Physical Activity and Cancer Survivorship pilot funding from the UNC Lineberger Comprehensive Cancer Center, Duke Cancer Institute and the Wake Forest Baptist Comprehensive Cancer Center.

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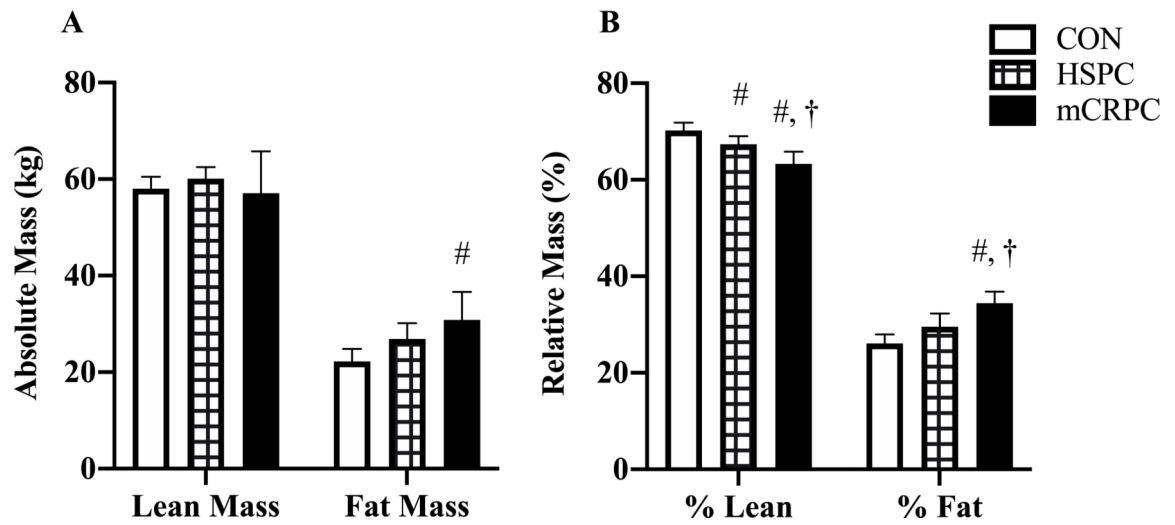


Figure 1.

Differences in **A**) absolute lean and fat mass and **B**) relative lean and fat mass in men with metastatic, castration-resistant (mCRPC, n=22) or hormone-sensitive prostate cancer (HSPC, n=42) and non-cancer controls (CON, n=37). Reported as mean \pm 95% CI.

P<0.05 vs, CON

† P<0.05 vs. HSPC

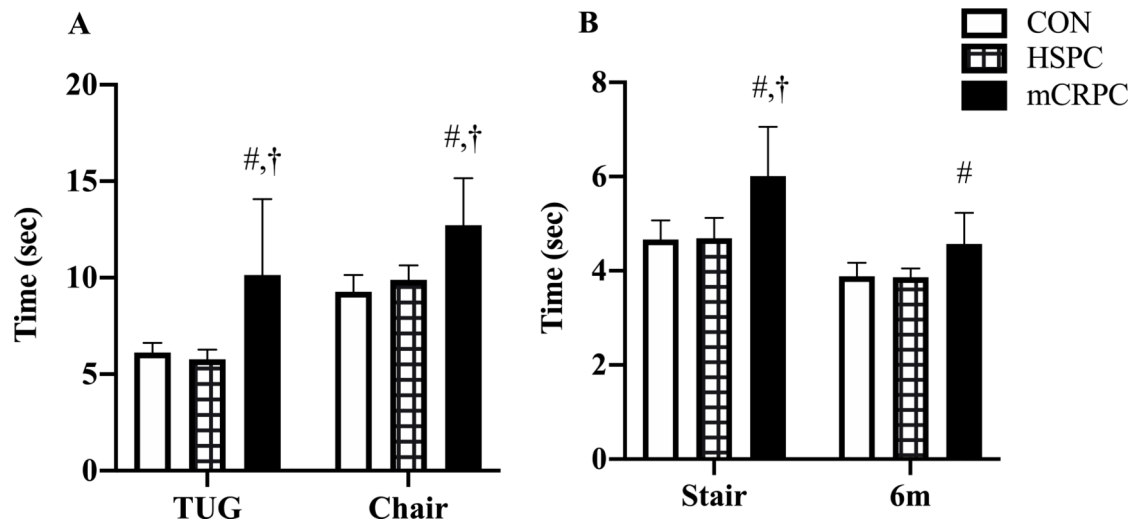


Figure 2.

Time to complete the **A)** timed up and go (TUG) and 5 chair stands and **B)** Stair climb and 6m walk in men with metastatic, castration-resistant (mCRPC, n=22) or hormone-sensitive prostate cancer (HSPC, n=17) and non-cancer controls (CON, n=27). Reported as mean \pm 95% CI.

P<0.05 vs, CON

† P<0.05 vs. HSPC

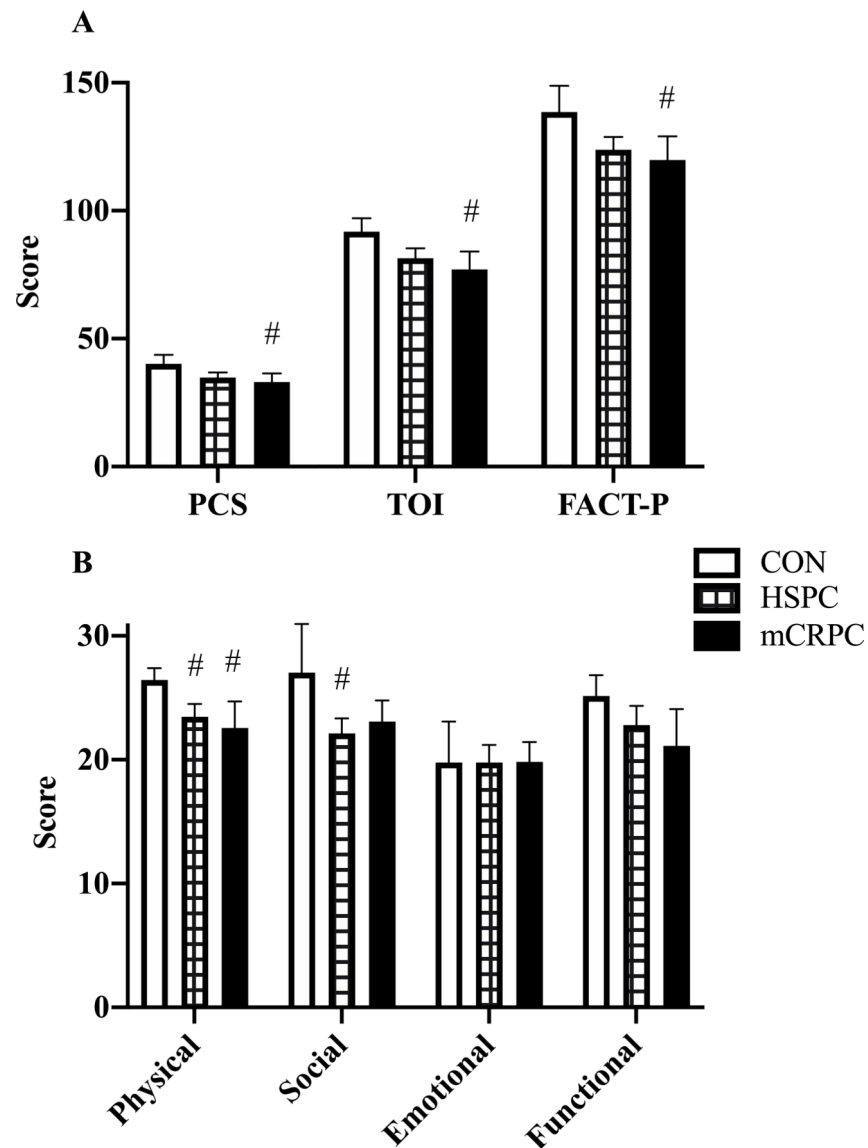


Figure 3. Quality of life assessment scored by **A**) Prostate Cancer Subscale (PCS), Trial Outcome Index (TOI), and Functional Assessment of Cancer Therapy-Prostate (FACT-P), along with the **B**) Physical, Social, Emotional and Functional Well-Being subscales in men with metastatic, castration-resistant (mCRPC, n=18) or hormone-sensitive prostate cancer (HSPC, n=42) and non-cancer controls (CON, n=11). Reported as mean \pm 95% CI. # P<0.05 vs. CON

Table 1.

Physical characteristics of men with mCRPC, HSPC and non-cancer controls.

	CON (n=37)	HSPC (n=42)	mCRPC (n=22)	P value
Age (years)	69 (6)	67 (6)	72 (8)	0.076
Height (cm)	174.9 (6.6)	171.5 (17.0)	175.0 (6.5)	0.324
Mass (kg)	83.3 (13.7)	90.7 (17.6)	91.4 (18.8)	0.099
Body mass index (kg/m ²)	27.1 (3.4)	32.2 (14.2)	29.8 (5.4)	0.101
Race				
Caucasian, n (%)	31 (84)	25 (59)	16 (73)	0.058
African American, n (%)	6 (16)	17 (41)	6 (27)	0.058
Previous prostatectomy, n (%)	-	15 (36)	11 (50)	0.269
Previous radiotherapy, n (%)	-	22 (52)	13 (59)	0.609
ADT Duration (months)	-	37 (38)	30 (34)	0.455
ARSI Duration (months)	-	-	6 (5)	-
Abiraterone n (%)	-	-	9 (41)	-
Enzalutamide, n (%)	-	-	8 (36)	-
Previous chemotherapy, n (%)	-	-	7 (33)	-
Time since chemotherapy (months)	-	-	16 (10)	-

Data are mean (standard deviation) or n (%). Abbreviations: HSPC=hormone-sensitive prostate cancer, mCRPC=metastatic castration-resistant prostate cancer, CON=non-cancer controls, ADT=androgen deprivation therapy, LHRHa=luteinizing hormone releasing hormone agonists, ARSI=androgen receptor signaling inhibitors

Table 2.

Correlations between body composition, physical function and quality of life.

	Lean	Fat %	Lean %	6m	Chair	TUG	Stair	PCS	TOI	FACT-P
Fat	0.540 **	0.861 **	-0.805 **	0.301 *	0.139	0.225	0.359 **	-0.055	-0.063	-0.036
Lean	-	0.197 *	-0.219 *	0.188	-0.109	0.051	0.184	-0.021	-0.009	-0.045
Fat %	-	-	-0.765 **	0.267 *	0.264 *	0.259 *	0.318 **	-0.122	-0.130	-0.115
Lean %	-	-	-	-0.305 *	-0.230	-0.321 **	-0.385 **	0.190	0.246 *	0.222
6m	-	-	-	-	0.364 **	0.766 **	0.844 **	0.118	0.121	0.171
Chair	-	-	-	-	-	0.103	0.342 **	-0.065	-0.043	0.032
TUG	-	-	-	-	-	-	0.833 **	0.055	0.075	0.139
Stair	-	-	-	-	-	-	-	-0.152	-0.081	-0.012

Lean=absolute lean mass; Fat=absolute fat mass; Lean %; relative lean mass; Fat %=relative fat mass; Chair=5 chair stands; TUG=timed up and go; Stair=stair climb; PCS= Prostate Cancer Subscale; TOI=Trials Outcome Index; FACT-P=Functional Assessment of Cancer Therapy-Prostate

*
p<0.05

**
p<0.01