A comparison of the sarcopenic effect of androgen receptor-axis-targeted agents vs. androgen deprivation alone in patients with metastatic prostate cancer

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ABSTRACT

Introduction: Androgen deprivation therapy (ADT) with androgen receptor axis-targeted (ARAT) therapy is the standard of care provided to patients with metastatic prostate cancer. While effective, it results in sequelae, such as loss of skeletal muscle mass. In this study, we compared the sarcopenic effects of abiraterone and enzalutamide, two ARATs used to treat metastatic prostate cancer.

Methods: Our cohort comprised of 55 patients diagnosed with metastatic hormone-naive prostate cancer from 2014–2019. Patients were divided into three treatment groups: gonadotropin-releasing hormone (GnRH) agonist alone; GnRH agonist combined with abiraterone acetate; and GnRH agonist combined with enzalutamide. We then compared axial computed tomographic (CT) scans at the L3 level before and after the initiation of hormone therapy for each patient. A skeletal muscle index (SMI) was calculated for each patient, and alongside clinical data, was compared between the three groups.

KEY MESSAGES

- ADT in combination with ARAT therapy is the standard treatment given to patients with metastatic prostate cancer.
- We compared the skeletal muscle loss experienced by patients taking either ADT alone or ADT in combination with either one of two ARATs (abiraterone or enzalutamide).
- We found that while all three groups experienced skeletal muscle loss, there was no significant difference in loss between the groups.

One-way analysis of variance (ANOVA) and Fisher's exact test were used to compare means and proportions, respectively.
Results: Baseline clinical characteristics were not significantly different between the three groups. The percent SMI change and number of newly sarcopenic patients were not found to be significantly different between the groups. The only variable that was significantly different across the three groups was time between CT scans.
Conclusions: Although we found no significant difference in the sarcopenic effects of GnRH alone, GnRH with abiraterone or GnRH with enzalutamide in our cohort of 55 hormone-naive metastatic prostate cancer patients, overall decreases in muscle mass was observed for all three groups. This highlights the importance of muscle-retaining strategies for patients undergoing ADT for metastatic prostate cancer, regardless of therapeutic regimen.

INTRODUCTION

Androgen deprivation therapy remains a cornerstone of treatment for patients with newly diagnosed metastatic prostate cancer. However, the addition of androgen receptor-axis-targeted therapies (ARAT) is now the standard of care based on multiple studies showing significant improvements in overall survival.[1]

This effective treatment does not come without significant potential side-effects. Decreased skeletal muscle mass (SMM) is a common side effect of ADT and is associated with adverse outcomes in cancer patients.[2] Androgens are vital anabolic drivers, leading to an accrual of muscle mass and decreased adiposity. Once deprived of androgens, the body enters a catabolic state, whereby depletion of muscle mass can lead to sarcopenia. Sarcopenia has been shown to correlate negatively with overall survival in several malignancies, including prostate cancer.[35] Given this, skeletal muscle loss needs to be considered for patients commencing ADT.

There are many studies in the literature looking at the impact of ADT on body composition. In an older study consisting of non-metastatic prostate cancer (nmPC) patients receiving GnRH agonist over 48 weeks, they found that percentage fat body mass increased by almost 10% and lean body mass decreased by 2.7%.[6] Another older study reported significant decreases in lean body mass amongst nmPC patients receiving ADT, with patients on acute ADT showing the greatest decrease.[7] The effects of abiraterone on body composition in conjunction with GnRH agonist has also been studied on patients with castration-resistant prostate cancer (crPC). In one study, patients who were treated for a median of 7.5 months with abiraterone had a significant decrease in muscle mass, which was notably maximal in those with a BMI of greater than 30.[8] Although there is information on the impact of combination ARAT-ADT on skeletal muscle mass, there is very little in the literature comparing ADT and ARAT therapies to ADT alone in hormone naïve metastatic prostate cancer patients. Herein, we aimed to directly

compare the sarcopenic effect of abiraterone and enzalutamide with ADT to ADT alone in metastatic prostate cancer patients.

METHODS

Patient selection & data collection

After ethics approval by our institutional research ethics board, we identified all patients diagnosed with metastatic hormone-naïve prostate cancer between 2014-2019 at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia. All included patients had received a computed tomographic (CT) scan of their abdomen prior to initiation of hormonal therapy, as well as throughout their hormonal therapy. All included patients had received one of three defined treatment regimens: (i) gonadotropin-releasing hormone (GnRH) agonist alone, or in concert with (ii) abiraterone acetate or (iii) enzalutamide. Patients were excluded from the study if they: had received previous ADT (N=9), had untimely death (within 6 months of therapy initiation) (N=1), received any other systemic therapeutic regimen not within our defined patient groups (N=4), did not have images of sufficient quality to assess SMM or both pre-treatment and post-treatment CT images (N=14).

Clinical and pathological data was collected from our institutional registry of prostate cancer patients and electronic medical records. Clinical data included age, height, weight, clinical T, N and M stages, pre- and post-treatment serum prostate-specific antigen (PSA), pre- and post-treatment serum testosterone, past medical history, previous cancer treatments (surgery, radiation, hormones) as well as current hormonal therapy.

Measurement of skeletal muscle mass

To measure SMM, patient pre- and post-hormone treatment initiation CT images were collected using IMPAX 6 (Agfa®; Mortsel, Belgium). Representative axial CT images from the L3 level were transmitted to the Slice-O-Matic 5.0 software (Tomovision®; Québec, Canada). Here, the cross-sectional area of skeletal muscle was measured for each patient using muscle-specific attenuation thresholds (-29 to 150 Hounsfield units) (Figure 1). The skeletal muscle index (SMI) was then calculated for each patient by dividing total skeletal muscle area at the L3 level by the patient's height squared. Based on international consensus, patients are defined as being sarcopenic if their SMI is < 55 cm^2/kg^2.[2] All body composition analyses were performed by a single investigator (K.M.R. using Slice-O-Matic 5.0 software; Tomovision, Quebec, Canada).

Statistical analysis

Patient characteristics, as well as clinical and pathological outcomes were compared across the three groups using one-way analysis of variance (ANOVA). Variables that had significant skew (greater than 1 or less than -1) and violated homogeneity of variances were compared using Welch's ANOVA. Variables that were skewed but did not violate homogeneity of variances were compared using the Kruskal-Wallis test and had medians reported. Changes in skeletal muscle mass were calculated by taking the difference between pre- and post-treatment muscle

masses and dividing by pre-treatment ("initial") muscle mass. The mean change in skeletal muscle mass and all other means were then compared across the three groups using one-way ANOVA. Fisher's exact test was used to compare the proportion of patients who had their prostate biopsied, as well as sarcopenic and newly sarcopenic patients across the three groups. We used $p<0.05$ as a threshold for statistical significance.

RESULTS

There were 83 patients identified who had a diagnosis of metastatic hormone-naïve prostate cancer between 2014-2019. 13 patients were excluded from the cohort as they had undergone previous ADT or received therapy not defined in our patient groups. One patient was excluded due to untimely death after initiating treatment. Additionally, another 14 patients were excluded due to lack of follow-up imaging or image quality. Thus, 55 patients with pre- and post-hormone treatment initiation CTs available for body composition analysis were included in this study (Table 1).

In all, 16 patients were included in the GnRH agonist group ("Group 1"); 29 patients were included in the GnRH agonist and abiraterone group ("Group 2"); and 10 patients were included in the GnRH and enzalutamide group ("Group 3"). Overall, the average age at time of diagnosis was 72.3 years and was not significantly different across groups. Pre-treatment PSA across all groups was 308.43 ng/mL and was not significantly different across the groups. With respect to SMI measurements, 38 men (69.1%) were found to be sarcopenic before the initiation of any hormone therapy. Percentage of patients who had their prostate biopsied was found to be the only baseline patient characteristic that significantly differed between groups ($P<0.05$).

Overall, 98.2% of our patients had de novo metastatic disease with only one patient developing metastatic disease following local therapy (Table 1). Using the CHAARTED trial definition,[21] 63.6% were found to have high volume metastatic disease. The ADT alone group (12.5%) had the lowest proportion of high volume disease.

In Table 2, we summarize post-hormone initiation results. Overall, the cohort's median PSA decline was 99.25% after the initiation of hormone therapy (p=0.89). Of the 17 patients who were non-sarcopenic before hormone therapy, 5 (27.8%) became sarcopenic with the initiation of hormones. Within the groups, 25% of non-sarcopenic patients in the GnRH group became newly sarcopenic with hormone therapy compared to 40% of non-sarcopenic patients in the Abiraterone group. Conversely, 0% (0/4) of non-sarcopenic enzalutamide patients became newly sarcopenic.

In Table 3, we highlight the results of SMI change throughout treatment. We found that the GnRH agonist group suffered a median SMI decline of 8.67% (mean of 7.33%), as compared to 5.23% (mean of 4.88%) for the abiraterone group and 7.30% (mean of 5.81%) in the Enzalutamide group. There was no significant difference in decline across the groups (p = 0.82). Given the widely variable time between successive CTs among the groups (p=0.051), we standardized the SMI decline per 1000 days. Using this measure, we can see that across the entire cohort, a median decline of 11.37 SMI units (mean of 12.25) would be expected over 1000

days. Within the groups, this decline would be 9.00 (mean of 11.09) for the GnRH group, 11.01 (mean of 12.92) for abiraterone and 17.18 (mean of 12.16) for enzalutamide. This again did not show a statistically significant difference between the groups ($p = 0.85$).

DISCUSSION

Age-related muscle loss is known to occur at an approximate rate of 1-2% per year after the age of 40 but becomes more pronounced after the age of 50.[9,10] Fat mass accrues in these years, up to age of 70, at which time it stabilizes or may even slightly decrease.[11] It is estimated that the prevalence of sarcopenia among elderly people aged 60-70 years is 5-13% whereas those aged 80 years and above have an estimated prevalence of 11-50%.[12,13] Sarcopenia has been identified as a poor prognostic factor among patients and plays an important role in frailty status.[14] Once ADT or ARAT therapy is initiated, sarcopenia is known to develop and progress within 90-180 days, with an eventual plateau thereafter.[18,19] Thus, in our study with a median follow-up of 335 days, we feel we have adequately captured the trajectory of sarcopenia in our patients.

Overall, we found an approximate 5-7% decline in SMI over the follow-up period in our patients. This in stark contrast to the expected annual muscle loss of 1-2% in men not on ADT, as described in the literature.[9,10] Furthermore, we identified that a significant proportion of our patients with newly diagnosed hormone naïve metastatic prostate cancer (69.1%) began treatment in a sarcopenic state based on the L3 SMI criteria. The established prevalence of sarcopenia in the literature for patients over 60 years old ranges from 10-50%.[20] Our appreciably higher proportion of nearly 70% prior to hormonal therapy may be explained by our patient cohort that was generally older (mean 72.5 years) and more comorbid (mean Charlson comorbidity index of nearly 10). We also found that a further 29.4% of patients who were non-sarcopenic at the onset of treatment became sarcopenic during their treatment. These findings highlight the importance of evaluating our patients' overall health and fitness prior to initiating hormone therapy as it is evident that this population could be facing considerable morbidity even before starting treatment that will likely further decrease their muscle mass.

When comparing skeletal muscle loss in our patients undergoing either GnRH agonism alone, or in combination with abiraterone or enzalutamide, we did not find any significant difference among the groups. This is an interesting finding, given the assumption that treatment intensification with an ARAT should have more profound sarcopenic effects. However, an explanation for statistically equal muscle loss across the groups may be their equally suppressive effects on testosterone levels. The average post-treatment testosterone level is 0.44 nmol/L for ADT alone, 0.15 nmol/L for abiraterone and 0.43 nmol/L for enzalutamide. All three groups were adequately castrated (defined as testosterone <1.7 nmol/L) with a clinically insignificant range of 0.29 nmol/L across the groups. This finding suggests that all therapeutic strategies are similar in their sarcopenic effects, further highlighting the net benefit of treatment intensification with ARAT therapy in these patients.

Strategies aimed at mitigating the loss of muscle mass during treatment may prove to decrease the potential morbidity associated with sarcopenia. At our local institution, our prostate cancer patients are offered access to a multidisciplinary exercise and wellness program at the time of their diagnosis. The observed improvements in patient quality of life and reduction in treatment-related adverse effects from this program are consistent with findings from other studies looking at resistance training protocols implemented for prostate cancer patients undergoing ADT.[15,16]

Our findings are confirmatory to those in a previous study by Fischer et al. comparing skeletal muscle loss in patients taking either abiraterone or enzalutamide. A significant decrease in skeletal muscle for both the abiraterone and enzalutamide groups as well as no significant difference in percent change of skeletal muscle between the two groups was observed.[17] While these findings were similar to ours, Fischer et al. examined ADT in combination with either abiraterone or enzalutamide and did not have ADT alone. Their study population also consisted of patients with metastatic castration-resistant prostate cancer as opposed to hormone naïve. Nonetheless, the decrease in skeletal muscle mass reported by Fischer et al. and our study highlights the sarcopenic effects of these two ARAT therapies in the setting of metastatic prostate cancer.

Several limitations to this study warrant consideration. First, the retrospective nature of this study introduces a potential selection bias between patients treated with ADT alone and those treated with ARAT therapy. If those receiving ADT alone were more prone to developing sarcopenia, this may reduce the difference between the groups leading to a false negative finding. Second, there was a wide variability in time between CT scans among the groups. We attempted to standardize the change in SMI over time by projecting their SMI loss over 1000 days. Using this metric, we again could not find a significant difference among the groups. Finally, the small number of patients in each group limits the statistical power to find a difference between groups.

CONCLUSIONS

In our study, we found that there was no significant difference in skeletal muscle loss for metastatic prostate cancer patients undergoing either GnRH agonism, or GnRH agonism in combination with either abiraterone or enzalutamide. This finding highlights the importance of skeletal muscle maintenance strategies and resistance training protocols in metastatic prostate cancer patients undergoing ADT, regardless of the therapy regiment they undertake.

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FIGURES AND TABLES

Figure 1. A demonstration of how skeletal muscle area was calculated using axial computed tomographic images at L3 Vertebra. The images depict the same patient at two distinct time points: (A) pre-initiation of androgen deprivation therapy (ADT) and (B) 6 months post-initiation of ADT. As can be seen, there is noticeable decrease in skeletal muscle mass after initiation of ADT.

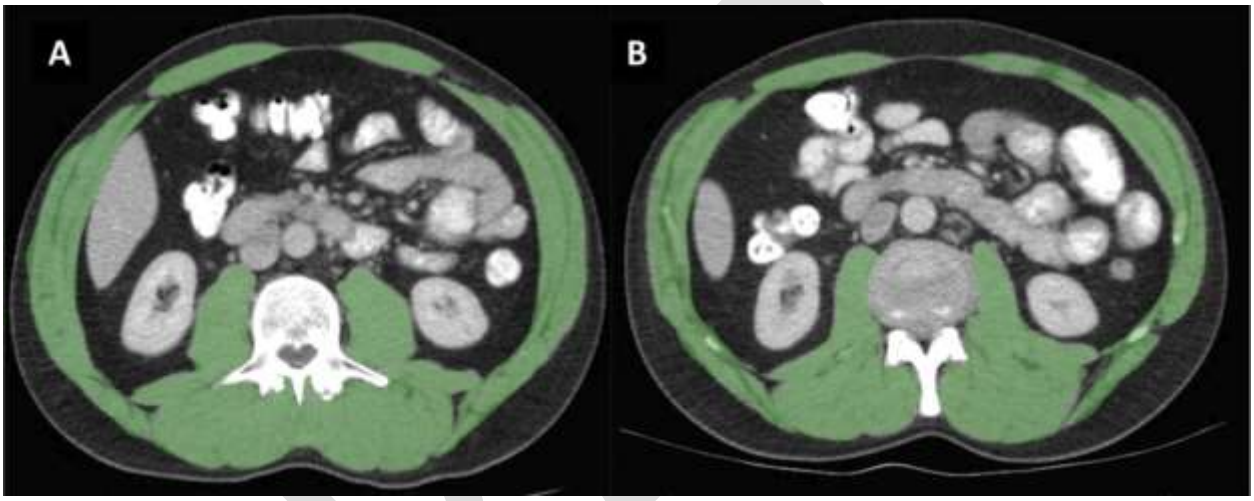

Table 1. Baseline characteristics of entire cohort and according to hormone therapy					
Characteristic	**Overall**	**GnRH**	**Abiraterone**	**Enzalutamide**	**p**
Total number, N	55	16	29	10	
Age at diagnosis (years), mean (SD)	72.33 (10.83)	72.46 (9.61)	72.41 (11.16)	71.93 (12.72)	0.99
Pretreatment SMI (cm^2/m^2), mean (SD)	50.67 (9.77)	52.08 (9.54)	49.20 (8.97)	52.68 (12.47)	0.50
Comorbidity index, mean (SD)	9.40 (1.65)	8.94 (1.18)	9.76 (1.88)	9.10 (1.50)	0.23
Pretreatment PSA (ng/mL), mean (SD)	308.43 (679.65)	160.32 (172.51)	433.88 (902.79)	166.78 (169.56)	0.31
Sarcopenic Patients, n (%)	38 (69.09%)	12 (75%)	19 (65.52%)	6 (60%)	0.80
Prostate biopsied, n (%)	34 (61.82%)	10 (62.50%)	14 (48.28%)	10 (100%)	<0.05
De novo metastatic, n (%)	54 (98.18%)	16 (100%)	29 (100%)	9 (90%)	0.18
High-volume disease*, n (%)	35 (63.64%)	2 (12.50%)	26 (89.66%)	7 (70%)	<0.05

n=1 missing from age at diagnosis and comorbidity index for rnzalutamide group. n=1 missing from pretreatment PSA for GnRH group. *As per the CHAARTED definition, high-volume disease was defined as presence of visceral metastasis or ≥4 bone lesions with ≥1 lesion beyond the vertebral bodies and pelvis. GnRH: gonadotropin-releasing hormone PSA: prostate-specific antigen; SD: standard deviation; SMI: skeletal muscle index.

Table 2. Post-hormone initiation outcomes of entire cohort and according to hormone therapy

Characteristic	Overall	GnRH	Abiraterone	Enzalutamide	p
Total number, N	55	16	29	10	
Posttreatment PSA (ng/mL), mean (SD)	3.99 (9.65)	7.86 (16.86)	2.64 (3.46)	1.70 (2.45)	0.32
PSA decline (%), median (mean, SD)	99.25 (95.43, 9.85)	99.08 (93.28, 10.83)	98.83 (95.81, 10.77)	99.36 (97.47, 4.90)	0.89
Newly sarcopenic patients, n (%)	5 (27.78%)	1/4 (25%)	4/10 (40%)	0/4 (0%)	0.57
Post-treatment SMI (cm^2/m^2), mean (SD)	47.62 (9.14)	48.03 (8.37)	46.73 (8.90)	49.55 (11.45)	0.69
Time between CTs (days), mean (SD)	333.36 (209.76)	460.19 (311.58)	293.03 (129.25)	247.40 (90.35)	0.051

n=1 and n=3 missing from post-treatment PSA for GnRH and abiraterone groups, respectively. n=2 and n=3 missing from PSA decline for GnRH and abiraterone groups, respectively. GnRH: gonadotropin-releasing hormone PSA: prostate-specific antigen; SD: standard deviation; SMI: skeletal muscle index.

Table 3. Skeletal muscle index changes of entire cohort and according to hormone therapy

Characteristic	Overall	GnRH	Abiraterone	Enzalutamide	p
Total number, N	55	16	29	10	
Pretreatment SMI (cm^2/m^2), mean (SD)	50.67 (9.77)	52.08 (9.54)	49.20 (8.97)	52.68 (12.47)	0.50
Post-treatment SMI (cm^2/m^2), mean (SD)	47.62 (9.14)	48.03 (8.37)	46.73 (8.90)	49.55 (11.45)	0.69
SMI change (%), median (mean, SD)	7.14% (5.76%, 8.72)	8.67% (7.33%, 8.48)	5.23% (4.88%, 9.79)	7.30% (5.81%, 5.61)	0.82
SMI (cm^2/m^2) change per 1000 days, median (mean, SD)	11.37 (12.25, 23.13)	9.00 (11.09, 19.60)	11.01 (12.92, 27.80)	17.18 (12.16, 12.78)	0.85

GnRH: gonadotropin-releasing hormone PSA: prostate-specific antigen; SD: standard deviation; SMI: skeletal muscle index.