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Quantifying the changes in body mass index and performance status during androgen deprivation therapy for advanced prostate cancer in southeast Nigeria

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Abstract

Background Androgen deprivation therapy (ADT) for advanced prostate cancer (aPCa) causes changes in body mass index (BMI) and in the performance status depending on the extent of cancer remission. The aim of this study is to quantify these changes.

Methods A prospective cohort study in a public tertiary urology centre in Enugu, southeast Nigeria. With appropriate sample size determined, men with aPCa for ADT, by surgical or medical modality, were recruited into a test group (TG), taking note of the Gleason score. A cohort of similar men without malignant or debilitating diseases formed the control group (CG). The age, weight and the Eastern Cooperative Oncology Group (ECOG) score were determined before ADT and at 2 monthly intervals for the TG. Same parameters were assessed for the CG at 2 monthly intervals. Additionally, total prostate-specific antigen (tPSA) was done for the TG at 3 monthly intervals.

Results In all, 119 men in the TG and 68 men in the CG were recruited with no differences in age (F 2.777; p 0.10) and height (F 0.409; p 0.52) at recruitment. In the TG, BMI increased from 25.20 ± 3.92 to 26.26 ± 3.90 kg/m^2 (p 0.001), median tPSA dropped from 36.9 ng/ml (IQR 20.4–65.7) to 3.7 ng/ml (IQR 1.1–8.7) and ECOG score improved (χ^2 34.1; df9; $p < 0.001$) with reduction in the proportion of men with ECOG > 1 from 84.0 to 20.4%. A secondary finding is that gains in BMI and in ECOG score are earlier in the surgical modality than in the medical modality of ADT.

Conclusions In the first 6 months of ADT, there are gains in BMI and ECOG scores. These gains are earlier with surgical modality of ADT.

Keywords Advanced prostate cancer, Androgen deprivation therapy, Body mass index, ECOG score, Performance status

1 Background

Clinical presentation with features of advanced prostate cancer is prevalent in many sub-Saharan African settings, including southeast Nigeria [1, 2]. These advanced stages of prostate cancer are usually associated with physical wasting, poor performance status and poor health-related quality of life [3–5]. Androgen deprivation therapy (ADT), therefore, has remained the prevalent first-line therapeutic strategy in these settings.

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Androgen deprivation therapy can be administered as a single therapeutic strategy or in combination with chemotherapeutic agents where the expected benefit from such combinations outweighs the possible toxicity [6, 7]. Undoubtedly, ADT alone is better tolerated, and it results in gradual improvement in clinical state in the hormone-sensitive prostate cancer [8, 9]. For instance, the study by Akpayak et al. [10] reports that ADT alone results in improvement in symptoms including lower urinary tract symptoms (LUTS) and in the quality of life due to LUTS.

A number of clinical and laboratory parameters could be used to evaluate progression of the prostate cancer patient during ADT [11]. The body mass index (BMI) and the level of physical activity assessed as performance status using instruments such as the Eastern Cooperative Oncology Group (ECOG) score are parameters expected to vary with ADT in prostate cancer [12, 13]. While prostate cancer aggressiveness and progression usually result in deterioration in BMI and level of physical activity [5], ADT induces cancer remission resulting in arrest of further deterioration and in some positive changes in these physical parameters [13]. In addition, serum total prostate-specific antigen (tPSA), a laboratory parameter is known to decline with prostate cancer remission during ADT to a nadir level [7, 14, 15]. In quantitative terms, however, the rate and extent of change in these physical and laboratory parameters during ADT for advanced prostate cancer in low resource sub-Saharan African setting needs to be examined.

An understanding in quantitative terms, of the variations in the BMI, ECOG score and tPSA will be of some benefit in the follow-up of these men. It will guide decision-making regarding frequency of hospital follow-up appointments and laboratory requests for tPSA assessment. This is important because direct out-of-pocket payment for care for cancers at all stages is prevalent in many of these low resource settings [16, 17]. This study therefore aims to determine in quantitative terms the variations in BMI, ECOG score and tPSA in the first 6 months of ADT for advanced prostate cancer.

2 Methods

This was a prospective cohort study conducted in a tertiary urology care centre in southeast Nigeria, an area according to national population figures of 2021 (www.nigerianstat.gov.ng; www.data.worldbank.org) with an estimated population of about 2.288 million men ≥40 years of age. The health facility administered ADT on approximately 158 men with advanced prostate cancer per annum in the last 3 years.

The variables of interest were the prostate biopsy Gleason score at diagnosis (GS), the serum total prostate-specific antigen (tPSA) prior to commencement of ADT modality of choice, the Eastern Cooperative Oncology Group (ECOG) score of physical activity level, and the patient's height and weight from which body mass index (BMI) values were determined.

Using an appropriate formula [18] $SS = \frac{2SD^2(Z_{\alpha/2}+Z_{\beta})^2}{d^2}$, and adopting a type I error of 5% ($Z_{\alpha/2}=1.96$), a statistical power of 80% ($Z_{\beta}=0.842$), an effect size $d=2$ kg/m^2 and correcting for a possible 10% attrition rate, the sample size SS determined for this study was 112 for the test group (TG) based on SD of 5.1 from Dalla Via et al. [12] in 2019.

From November 2020 to September 2021, patients that met inclusion criteria were recruited with their informed consent. There was no randomization. Upon recruitment, the GS was noted. In the week preceding commencement of participant's preferred ADT, tPSA, ECOG score and BMI were determined as the baseline values. Subsequently, at 2 monthly intervals, BMI and ECOG score were re-determined, while at 3 monthly intervals, tPSA was re-determined.

At the same period, men of similar age group who were attending the same hospital for non-malignant, non-debilitating disease conditions mostly uncomplicated benign prostate hyperplasia (BPH) and hypertension were recruited as control group (CG) for serial BMI and ECOG score assessments.

Participants exited the study at the end of 6 months of ADT, upon withdrawal of consent, or at death or loss to follow-up. Descriptive statistics were obtained for the variables. The means of the study variables in the two groups and at the different times during observation were compared using paired t test. The changes in each variable in the TG were quantified in percentages. Trend analyses were done to depict the aggregate rate of change in each variable of interest in 6 months. The few cases of missing data were handled by determining mean of available data for that variable. All analyses were done using SPSS version 21 (IBM Co., Armonk, NY, USA). The bioethics committee of the University of Nigeria Teaching Hospital approved of the study.

3 Results

The test group (TG) had 119 participants, while the control group (CG) had 68 participants at baseline. Figure 1 shows the number of participants at specific periods during the study. There was no significant difference in age (F 2.777; p 0.10) and height (F 0.409; p 0.52) of participants in the TG and in the CG at baseline.

Baseline figures showed that at recruitment, the physical performance of 19 (16.0%) participants in the TG was ECOG ≤1, while the physical performance of all participants in the CG was ECOG ≤1. Within the TG, the median tPSA at recruitment was 34.50 ng/ml (IQR

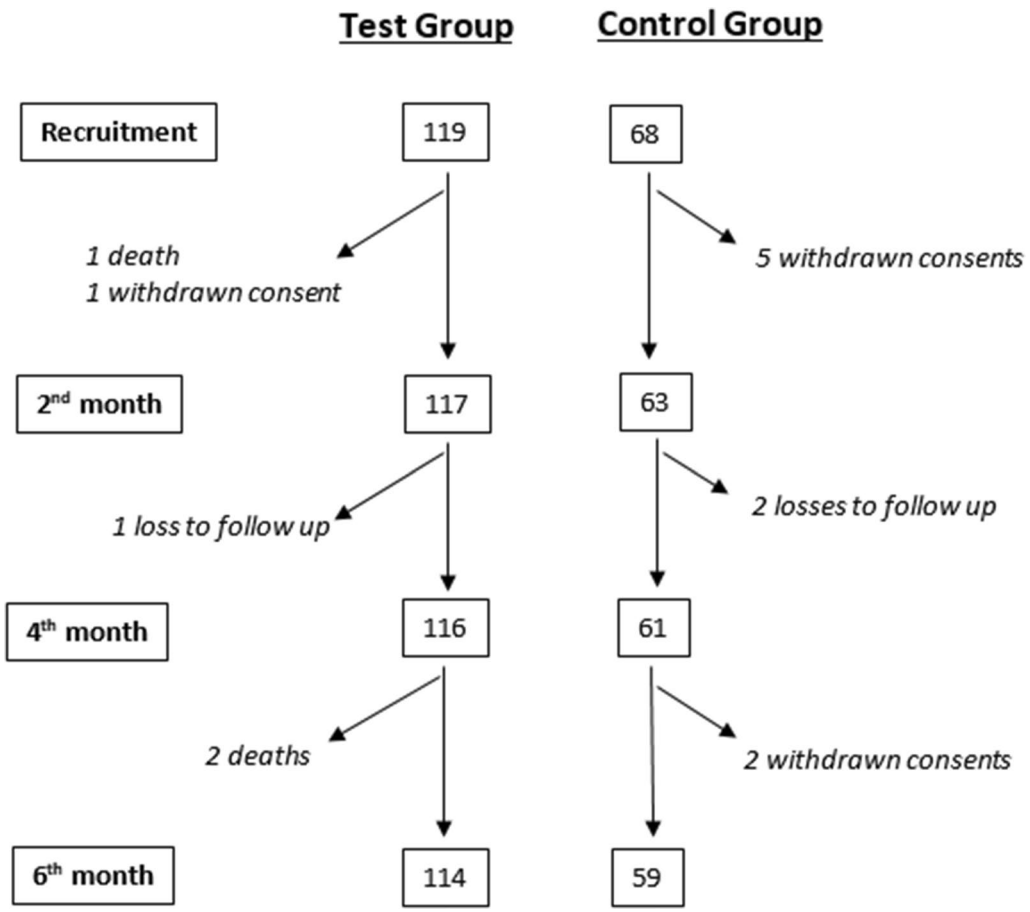

Fig. 1 Graphic representation of number of study participants

Table 1 Baseline descriptive statistics for the test (ADT) group and the control group

Variables	Test group	Control group
Mean age (years)	67.48 ± 8.64	65.41 ± 7.23
Mean height (m)	1.63 ± 0.11	1.64 ± 0.11
Mean weight (kg)	66.71 ± 10.36	68.66 ± 10.976
Mean BMI (kg/m^2)	25.12 ± 3.83	25.62 ± 4.58
Median tPSA (ng/ml)	34.50 (IQR 20.10–65.70)	

GS Gleason score; *BMI* body mass index; *tPSA* serum total prostate-specific antigen

20.10–65.70), and the International Society of Urological Pathology (ISUP) grade distribution was ISUP 1 = 12 (10.1%), ISUP 2 = 9 (7.6%), ISUP 3 = 13 (10.9%), ISUP 4 = 37 (31.1%), and ISUP 5 = 48 (40.3%). Table 1 describes further the dataset at recruitment for the test group (TG) and control group (CG).

In the test group, 28 (23.5%) opted for medical orchidectomy using gonadotropin-releasing hormone analogue (GnRHa). There was no difference in BMI (F 0.00; $p > 0.99$), in ISUP grade (χ^2 2.64; df 4; p 0.62) and in tPSA (F 1.95; p 0.17) of participants in GnRHa and BTO subgroups. The weight, BMI, and ECOG values are obtained at 2 monthly intervals, and the serum tPSA at 3 monthly intervals are shown in Table 2.

Deploying trendlines, the behaviour of mean serum total prostate-specific antigen (Fig. 2), mean body mass index (Fig. 3) and the proportion of participants demonstrating ECOG > 1 (Fig. 4) during the first 6 months of ADT are displayed.

The mean tPSA dropped rapidly by 75.9% in the first 3 months, but slowed to a value of 45.7% in the second 3 months for the GnRHa subgroup. The corresponding figures for the BTO subgroup were 69.5% and 41.0% in the same periods.

Specifically, for the GnRHa subgroup, there was no increase in mean BMI in the first 2 months. However, the mean BMI increased by 1.6% in the second 2 months and continued by that same value of 1.6% in the third 2 months. The corresponding values for the BTO subgroup were 1.2% in the first 2 months, 2.0% in the second 2 months and 1.9% in the third 2 months.

Table 2 Variation in the mean weight, mean BMI, mean tPSA and the proportion of participants with ECOG scores > 1 for the GnRHa subgroup, BTO subgroup and the control group

Variable	Timing	GnRHa (*p* value)	BTO (*p* value)	Control (*p* value)
Mean weight (kg)	Inception	65.7 ± 9.6	67.0 ± 10.7	68.6 ± 11.2
	2nd month	65.9 ± 9.3 (*p* 0.41)	67.8 ± 10.5 ($p < 0.001$)	68.6 ± 11.2 (*p* 0.52)
	4th month	67.0 ± 9.8 (*p* 0.007)	69.0 ± 10.5 ($p < 0.001$)	68.7 ± 11.0 (*p* 0.48)
	6th month	67.8 ± 10.0 (*p* 0.001)	70.2 ± 10.7 ($p < 0.001$)	68.7 ± 11.0 (*p* 0.22)
Mean BMI (kg/m^2)	Inception	25.2 ± 5.2	25.1 ± 3.4	25.5 ± 4.6
	2nd month	25.2 ± 4.9 (*p* 0.79)	25.4 ± 3.4 ($p < 0.001$)	25.5 ± 4.6 (*p* 0.46)
	4th month	25.6 ± 5.1 (*p* 0.004)	25.9 ± 3.4 ($p < 0.001$)	25.5 ± 4.6 (*p* 0.41)
	6th month	26.0 ± 5.2 ($p < 0.001$)	26.4 ± 3.5 ($p < 0.001$)	25.5 ± 4.6 (*p* 0.24)
Proportion with ECOG score > 1 (%)	Inception	85.7%	83.5%	
	2nd month	72.0% (*p* 0.001)	46.2% ($p < 0.001$)	
	4th month	33.3% ($p < 0.001$)	34.8% ($p < 0.001$)	
	6th month	25.0% ($p < 0.001$)	19.0% ($p < 0.001$)	
Mean tPSA (ng/ml)	Inception	38.2 ± 23.3	47.2 ± 33.0	
	3rd month	9.2 ± 6.9 ($p < 0.001$)	14.4 ± 19.2 ($p < 0.001$)	
	6th month	5.0 ± 3.4 (*p* 0.001)	8.5 ± 16.2 ($p < 0.001$)	

GnRHa gonadotropin-releasing hormone analogue; *BTO* bilateral total orchidectomy; *BMI* body mass index; *ECOG* Eastern Cooperative Oncology Group; *tPSA* serum total prostate-specific antigen

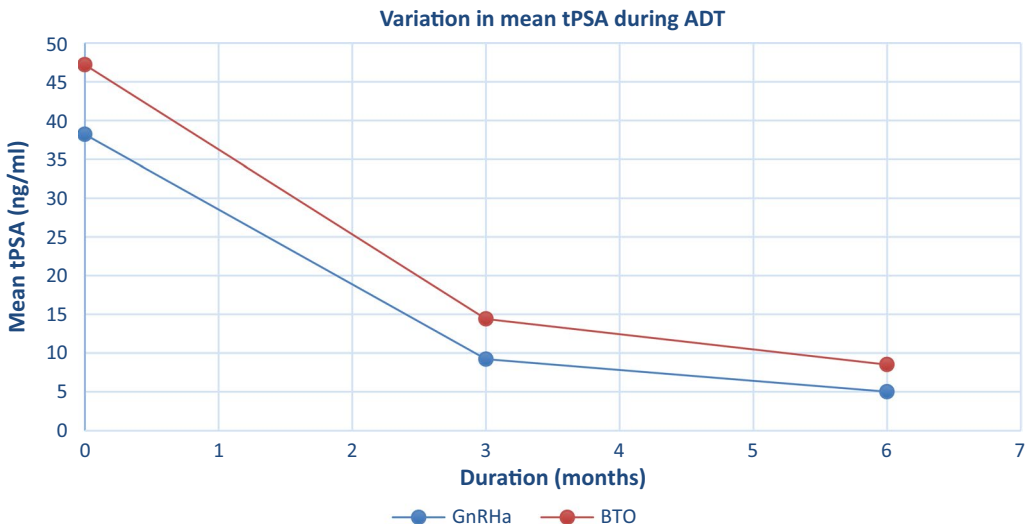

Fig. 2 Variation in mean tPSA during ADT

Specifically, in the GnRHa subgroup, the proportion of men adjudged ECOG >1 decreased by 16.0% in the first 2 months, by another 53.8% in the second 2 months and by yet another 24.9% in the third 2 months. The corresponding values for the BTO subgroup were 44.7%, 24.7% and 45.4%, respectively.

4 Discussion

In our low resource setting, use of ADT is common, and in the absence of randomization as in this observational study, bilateral total orchidectomy is more frequently the preferred ADT strategy of choice. This finding of prevalent use of surgical orchidectomy is similar to findings

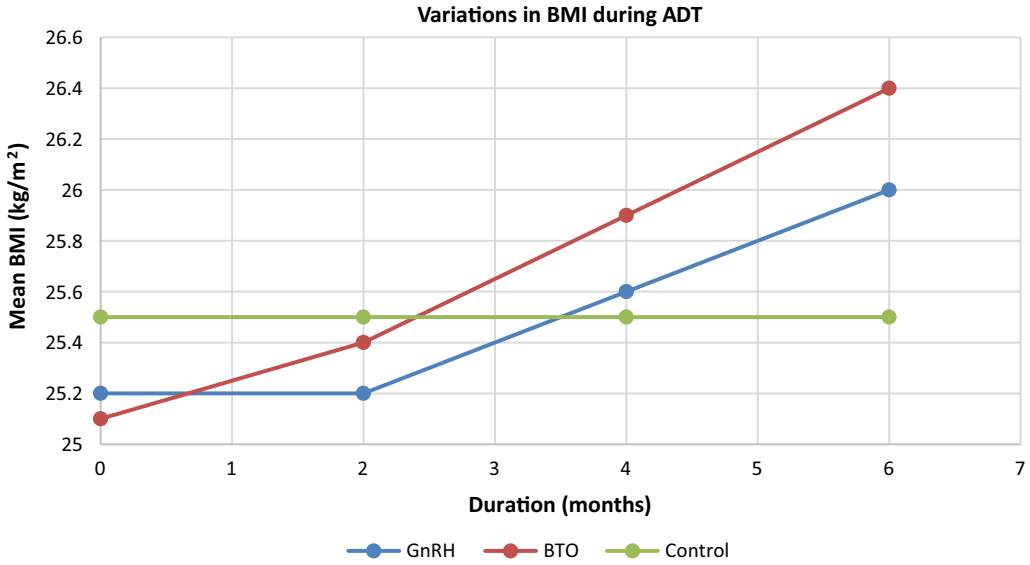

Fig. 3 Pattern of variation in BMI in the first 6 months of ADT

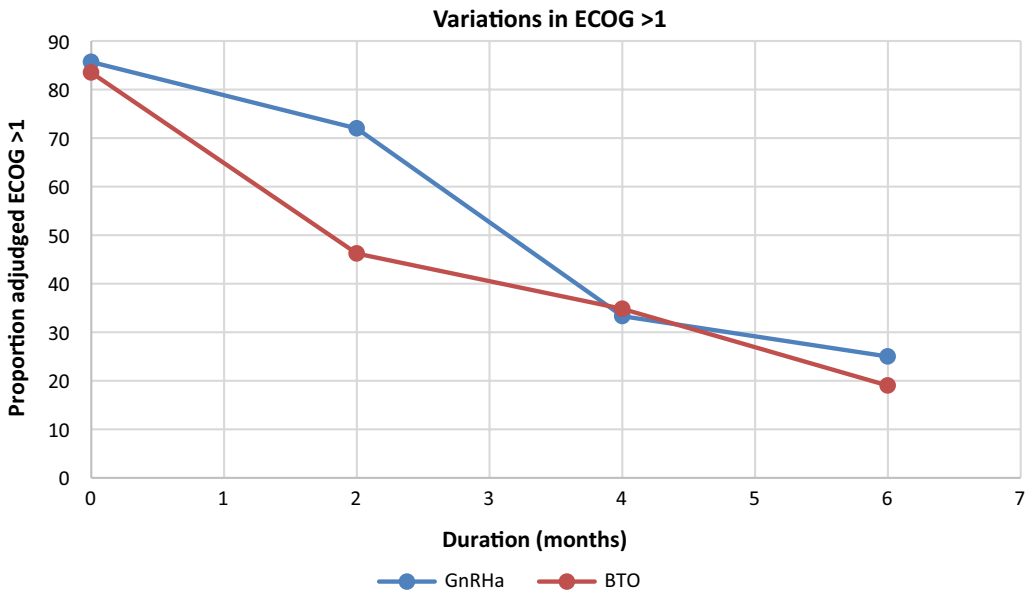

Fig. 4 Variations in the proportion of persons with ECOG > 1

from similar studies, and it is attributable to high cost and unavailability of gonadotropin-releasing hormone analogues [2, 19]. Generally, ADT results in an objective decline in tPSA to a nadir level during cancer remission [7, 14]. From other studies, the nadir tPSA level is reached at variable times during ADT and remains for a variable duration when so reached [14, 15]. In this study, the mean tPSA of 44.97 ± 31.13 ng/ml (median 34.50 ng/ml {IQR 20.10–65.70}) at recruitment (Table 1) is seen to decline gradually over this 6-month period as expected with cancer remission. During this period of remission, there are also reductions in the proportions demonstrating poor performance status and gains in the body mass index [13, 20].

However, of particular interest from this study are the pattern of change in the parameters of interest during the study period. Within the first 3 months of ADT by any of the two strategies, the tPSA had significantly declined. The decline is by a factor of 75.9% for the GnRHa subgroup ($p < 0.001$; Table 2; Fig. 2) and by 69.5% for the

BTO subgroup ($p < 0.001$; Table 2; Fig. 2). At about the same period, there is no evidence (p 0.79) that BMI had increased for the GnRHa subgroup, unlike in the BTO subgroup where it is observed that BMI had already increased significantly ($p < 0.001$; Table 2; Fig. 3). This is similar to the report by Østergren et al., (2019) that compared BTO with triptorelin, a gonadotropin-releasing hormone analogue [21]. It can be seen also from this study that a further drop in BMI from time of first dose of gonadotropin-releasing hormone analogue occurred prior to the anticipated gain akin to the report in 2016 by van den Driesscheet al. from Belgium [22].

Further drop in the tPSA by the 6th month is of reduced proportions in the two subgroups (Table 2; Fig. 2), but at this 6th month period, the additional gain in BMI is of increased proportions in both subgroups (Table 2; Fig. 3). From these figures, and on the premise that tPSA behaviour during ADT for advanced prostate cancer can reflect cancer cell behaviour [14, 15, 23], it appears that cancer remission is similar with both ADT strategies. However, onset of weight gain is earlier, and magnitude of weight gain is more with surgical orchidectomy (Table 2; Fig. 3). Of course, the reason for this finding is not decipherable from this study design, but may be related to differences in the effect of androgen deprivation on fat, muscle and bone metabolism for the two modalities of ADT.

Despite the finding from Fig. 4 of this study that the proportion of participants with ECOG scores greater than 1 had decreased significantly by the 4th month observation in the two subgroups, this study demonstrates that this decrease occurred remarkably earlier with bilateral total orchidectomy. It is observable within the GnRHa subgroup that the lag seen with weight (and BMI) gain is also seen with improvement in physical performance. In a low resource setting, improving physical performance may be positively related to gain in BMI during ADT for advanced prostate cancer. In addition, the gain in physical performance appears to be more sustained with bilateral total orchidectomy (Fig. 4). In comparison, a closer look at the results from the work by Bonfill et al. reported in 2021 shows that there is initially a slight decrease in the proportion of men on ECOG > 1 within the first 6 months of hormonal therapy, but this gain in physical performance is reversed by the 12 months of hormonal therapy [24].

The observation that the participants in the two subgroups are similar in terms of ISUP grade and tPSA at inception suggests that the observed differences in the pattern of gain in body mass index and of physical performance may not be explained by any difference in cancer cell biology. Immediate drop of testosterone to castrate levels with BTO as against a more gradual decline with GnRHa administration is a likely explanation for the observations [25, 26]. In a low resource setting in sub-Saharan Africa, BTO may not just be an efficient strategy [2], but may be a more effective strategy for ADT especially in clinical situation where prompt remission of symptoms is needed such as to avert paraplegia. In line with the recommendation by Aragon-Ching and Dreicer [27], 2020 that choice of agent for ADT be guided by factors such as burden of disease, co-morbidities and performance status, the need for prompt remission of symptoms could be a factor to also consider.

5 Conclusion

In this low resource setting, BTO is a more frequently deployed ADT strategy. Both BTO and GnRHa result in commensurate decline in tPSA values in the first 3–6 months, but the onset of gain in body mass index and of improvement in physical performance is earlier with BTO than with use of GnRHa. It is also likely that the extent of gain in BMI and in physical performance is higher with BTO than with GnRHa. The implication is that in situations of very late presentation with immediate threats to life or to spine, in advanced hormone-sensitive prostate cancer, BTO may be preferred as a strategy for prompt induction of cancer remission.

Abbreviations

ADT	Androgen deprivation therapy
aPCa	Advanced prostate cancer
BTO	Bilateral total orchidectomy
BMI	Body mass index
ECOG	Eastern Cooperative Oncology Group
GnRHa	Gonadotropin-releasing hormone analogue
tPSA	Total prostate-specific antigen

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Author contributions

LTO contributed in the conception and design of the study, in patient recruitment, data acquisition and analysis, in drafting the manuscript. IIN contributed in the conception and design of the study, in patient recruitment, data analysis and interpretation, and in revising the draft manuscript. KNE contributed in patient recruitment, in data acquisition and analysis, and in revising the draft manuscript. ONA contributed in patient recruitment, data analysis and interpretation, and in drafting the manuscript. SKA contributed in the conception of the study, in patient recruitment and data acquisition, and in drafting the manuscript. FOO contributed in the design of the study and in patient recruitment, in data analysis and in revising the draft manuscript. All authors read and approved of the final version of the manuscript being submitted.

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Availability of data and materials

The dataset generated during this study and analysed in this manuscript is available at Mendeley Data® https://doi.org/10.17632/267nm35jps.1.

Declarations

Ethics approval and consent to participate

The Health Research Ethics Committee of the University of Nigeria Teaching Hospital reference number NHREC/05/01/2008B-FWA00002458-IRB00002323 approved of this study. Written informed consent was obtained from all study participants. All experiments were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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