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Effect of Adding Metformin to The Combined Androgen Deprivation Therapy as Frontline Treatment in Metastatic Hormone-Sensitive Prostate Cancer Patients

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ABSTRACT

Background: Lack of physical activity and high body mass index (BMI) is linked to the aggressiveness of prostate cancer due to alteration of circulating levels of metabolic and sex hormones with reduced glucose uptake that led to the development of insulin resistance.
Objective: evaluate the effect of adding metformin to the combined androgen-deprivation therapy (ADT) in metastatic cancer prostate patients.

Patients and methods: Patients were included if having a diagnosis of Stage IV prostatic adenocarcinoma, No prior use of ADT, chemotherapy, and no prior use of metformin or other diabetes mellitus treatment. Both study groups received Combined ADT in the form of bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonists; Goserelin 3.6 mg subcutaneous q28 days with Bicalutamide 50 mg PO daily. In the Trial arm, Metformin was administered as metformin 1000 mg/twice daily. Patients were monitored monthly for compliance, safety. Prostatic specific antigen (PSA) level, random blood glucose, body weight, and drug-related side effects were evaluated every 3 months Disease progression was evaluated every 6 months.

Results: the addition of metformin to (ADT) in our study showed improvement of progression-free survival 39 months vs 30 months**,** PSA response at 9 months, and radiological response at 9 months were factors correlating with better PFS. There was an improvement in the quality-of-life assessment.

Conclusion: metformin should be considered as an effective agent to be used in combination with standard treatments for prostate cancer. The present study showed that Metformin use was associated with improved PFS and OS.

Keywords: Hormone-sensitive metastatic prostate cancer, Androgen deprivation therapy, Metformin.

INTRODUCTION

The country-specific data source of Egypt for the period (2006-2015) documented that prostate cancer ranks fourth most common cancer in males after cancer liver, bladder, lung, and it represents 7.2% and is responsible for 2.5% of cancer-related mortality of all malignant tumors in men [(1)].

Treatment of metastatic prostate cancer can be divided into 2 categories, treatment of metastatic hormone-sensitive prostate cancer (mHSPC) and treatment of metastatic castrate-resistant prostate cancer (mCRPC), when cancer has progressed on ADT [(2)].

Obesity, lack of physical activity, and high body mass index (BMI) are linked to the aggressiveness of prostate cancer and worse outcome due to alteration of circulating levels of metabolic and sex steroid hormones with reduced glucose uptake led to the development of insulin resistance resulting in chronically elevated blood levels of insulin [(3)].

Serum glucose is controlled by insulin, the high level of circulating insulin decreases the production of insulin-like growth factor (IGF-1)-binding proteins, The IGF system regulates many important cellular processes critical for normal prostate growth and development, such as proliferation, differentiation, and cellular metabolism; Increased serum concentration of IGF-1 was correlated to a higher risk of prostate cancer [(4)].

Metformin exerts direct effects as a metabolic homeostasis regulator and indirect effects as an anti-proliferative and anti-carcinogenic agent. Considering the potential association between metabolic syndrome and prostate cancer development and progression, metformin may be considered an adjuvant agent in combination with other therapies [(5)].

The study aimed to evaluate the addition of metformin on response rate, time to progression of PSA, progression-free survival, toxicity of the drug, overall survival, and the quality of life of the patients.

PATIENTS AND METHODS

This is a phase II prospective double-arm case-control study to evaluate the effect of adding metformin to the combined androgen-deprivation therapy (ADT) in metastatic cancer prostate patients treated at the clinical oncology department, Menoufia University.

Inclusion criteria:

Histological diagnosis of prostatic adenocarcinoma, Stage IV disease, with WHO P.S ≤ 2. No prior use of ADT, chemotherapy, and no prior use of metformin or other diabetes mellitus treatment.

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Exclusion criteria:

Patients with diabetes mellitus, advanced renal, hepatics, or cardiac disease. All patients were initially evaluated by Physical examination, Complete blood count, Chemistry profile, glycosylated hemoglobin (HbA1c), random blood glucose, baseline PSA levels, CT chest, abdomen, pelvis with contrast, and bone scan.

A total of 132 patients was recruited from May 2016 till December 2018, patients were randomly assigned (1:1) to either the trial group or control group by generating random numbers using computer software. **Group I (trial arm):** This arm included 66 patients. Those patients had received metformin together with the standard combined ADT; Metformin was administered 1000 mg/twice daily in uninterrupted 4-weeks cycles the dose increased stepwise (500-mg steps) within 2 weeks to the target dose concomitantly with combined ADT continuously till disease progression, drug toxicity or patient withdrawal. Combined ADT in the form of bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonists; Goserelin 3.6 mg SC q28 days with antiandrogen Bicalutamide 50 mg PO daily, antiandrogen started at least 7 days before commencing treatment with an LHRH analog. **Group II (control arm):** This arm included 66 patients; Those patients had received combined ADT.

Both groups received supportive treatment also involved palliative radiotherapy, bone-targeted agents (zoledronic acid 4mg I.V infusion q28 days), and other supportive measures if needed.

Patients were monitored monthly for compliance with treatment safety. PSA level, random blood glucose, body weight, and drug related-side effects (according to CTCAE (National Cancer Institute Common Terminology Criteria) for Adverse Events v.5) were evaluated every 3 months Disease progression was evaluated every 6 months by radiology work. The quality of life was assessed by using (FACT-P) Functional Assessment of Cancer Therapy – Prostate for patients with Prostate cancer (FACT-p version 4) as a baseline, 6 months, and after 1 year of therapy. The questionnaires were administered at the clinic. All patients provided written informed consent. This study was approved by the ethical committee of Human Rights in Research at Menoufia University.

Ethics approval and consent:

Approval of the study was obtained from Menoufia University academic and ethical committee. Every patient signed informed written consent for the acceptance of the operation. This work was carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed, and analyzed using the SPSS (Statistical Package for Social Sciences) version 20 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi 2$) to calculate the difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P-value < 0.05 was considered significant.

RESULTS

132 patients were randomized to either trial group or control group. The median follow-up duration for both studied groups was 36 months (95% CI, 25.8-46.1). The age of the studied cases ranged between 53 and 88 years with a median age of 70 years. There was no statistically significant difference in clinical and demographic characteristics between both study groups regarding age, smoking history, symptoms at presentation, performance status, pretreatment measuring of HbA1C, and the presence or absence of skeletal-related events.

There was no statistically significant difference between study groups regarding tumors characteristics **(Table 1).**

Table (1): Demographic and clinical data of both study groups

Studied variables	Studied groups		Test of sig.	P-value
	Group I Trial arm (N=66)	Group II Control arm (N=66)		
Age / years			t-test	
Mean ±SD.	69.5±9.27	70.6±9.45	0.725	0.470
Range	53 - 88	53 - 88		
Symptoms at Presentation				
Asymptomatic	6(9.10)	7(10.6)		
Irritative symptoms	29(43.9)	31(47.0)	X2=0.390	0.942
Obstructive symptoms	10(15.2)	8(12.1)		
Bone aches	21(31.8)	20(30.3)		
HBA1C baseline				
Mean ±SD.	4.80±0.67	4.76±0.74	0.450	0.653
Median	5.00	5.00		
Skeletal related events				
Present	45(68.2)	43(65.2)	0.136	0.712
Absent	21(31.8)	23(34.8)		
Gleason score				
Low	5(7.60)	6(9.10)	X2=	
Intermediate	27(40.9)	23(34.8)	0.538	0.764
High	34(51.5)	37(56.1)		
Disease volume				
Low	14(21.2)	16(24.2)	0.17	0.677
High	52(78.8)	50(75.8)		
Site of metastasis				
Bone metastasis only	47(71.2)	49(74.2)		
Visceral metastasis	8(12.1)	4(6.10)	1.54	0.463
Both (bone & visceral)	11(16.7)	13(19.7)		
Visceral metastasis				
Bone metastasis only	47(71.2)	49(74.2)		
Liver	3(4.50)	2(3.00)		
Lung	6(9.10)	8(12.1)	3.82	0.575
Liver & lung	4(6.10)	1(1.50)		
Soft tissue	1(1.50)	3(4.50)		
Extra regional LN	5(7.60)	3(4.50)		
Number of bone lesion				
Visceral metastasis	8 (12.1)	4 (6.10)		
< four lesions	18(27.3)	21 (31.8)	1.57	0.455
≥ Four lesions	40 (60.6)	41 (62.1)		
Baseline PSA			0.344	0.731
Mean ±SD.	321.1±313.5	312.7±328.6		
Median	184.5	153		

Most of the patients in both arms had high disease volume according to latitude and charted risk criteria [(6)]. The Median PSA among the patients at the start of the present study was 181ng /ml ranging from 10-998 ng/ml.

The pretreatment median PSA was 184.5 ng/ml in the trial arm and 153 ng/ml in the control arm. after 3 months of treatment, the median PSA measures After 6 months of treatment were 2.75 ng/ml and 4.20 ng/ml with statistically significant difference P-value (0.008) between both groups, and during follow up period of the study the mean PSA was lower in the trial arm compared to mean of PSA in the control arm at 3,6,9,12 months and at the end of follow up **(Table 2).**

Table (2): Prostatic specific antigen (PSA) measures among both groups during follow-up

PSA level	Studied groups		X^2	P-value
	Group I Trial arm (N=66)	Group I Trial arm (N=66)		
	N (%)	N (%)		
PSA at 3 months				
PR	65 (985)	65(985)		
SD	1 (1.50)	1(1.50)	0.00	1.00
PSA at 6 months				
CR	1 (1.50)	1(1.50)		
PR	62 (93.9)	61(92.4)		
SD	2 (3.00)	2(3.00)	0.341	0.952
PD	1 (1.50)	2(3.00)		
PSA at 9 months				
CR	11 (16.7)	5(7.60)		
PR	43 (65.2)	36(54.5)		
SD	10 (15.2)	12(18.2)	13.1	**0.004****
PD	2 (3.00)	13(19.7)		
PSA at 12 months				
CR	26 (39.4)	19(28.8)		
PR	20 (30.3)	10(15.2)		
SD	10 (15.2)	15(22.7)	9.92	**0.019***
PD	10 (15.2)	22(33.3)		
PSA at end of follow up				
CR	22 (33.3)	9(13.8)		
PR	14 (21.2)	11(16.7)		
SD	11 (16.7)	12(18.2)	10.0	**0.018***
PD	19 (28.8)	34(52.3)		

During follow-up median random blood glucose level, in the trial arm showed lower levels than the control arm. The minimum level measured was 61 mg/dl in the trial arm with no symptoms of hyperglycemia and the maximum level measures in the control arm were 132 mg/dl and there was a statistically significant difference between both groups at 9& 12 months with (P-value = 0.001). The BMI profile in the trial arm ranged from normal weight to class II obesity and ranged from normal weight to class III obesity in the control arm in the pretreatment assessment; while during the follow-up assessment there was a reduction in the range of BMI in the trial arm compared to control arm with a statically significant difference at 3,6,12 months and at the end of follow up (P-value 0.049, 0.005,0.001, 0.001) respectively.

Treatment data and clinical outcomes:

During follow-up of the study there was a statistically significant difference in response rate after 6th, 9th and at the end of follow up with (P-value 0.036, 0.010 & 0.002) between both study groups, respectively. After a median follow-up duration of 36 months, Progression occurred in 19 patients (28.8%) in the trial arm and 34 patients (48.5%) in the control arm, respectively

Until the end of the present study, (77.3%) were alive, while (54.5%) were alive, in the control arm P.Value 0.006

Toxicity assessment:

The trial arm showed a lower incidence of toxicity related to ADT with a statistically significant difference between both groups with (P-value =0.001)

As regards the toxicity profile of ADT among both groups the toxicities ranged from grade I to grade II, with increased incidence in the control arm for the prescribed toxicities shown in **(Table 3)** except for diarrhea and bloating which had more incidence in the trial arm.

There was a statistically significant difference of increased hot flushes, edema, weight gain, and diarrhea with (P-value 0.017,0.021,0.001 and 0.038).

Table (3): Toxicity related to treatment among the studied groups (N = 132)

Side effects		Studied groups		X^2	P-value
		Group I Trial arm (N=14)	Group II Control arm (N=38)		
		N (%)	N (%)		
Hot flushes	Grade I Grade II	11(78.6) 1(7.10)	13(34.2) 9(23.7)	8.10	**0.017***
Edema	Grade I Grade II	0(0.00) 0(0.00)	13(34.2) 2(5.30)	7.76	**0.021***
Weight gain	Grade I Grade II	0(0.00) 0(0.00)	19(50.0) 0(0.00)	11.0	**0.001****
Fatigue	Grade I Grade II	4(28.6) 0(0.00)	5(13.2) 1(2.60)	1.98	0.372
Nausea	Grade I Grade II	4(28.6) 2(14.3)	3(7.90) 1(2.60)	6.98	**0.030***
Gastritis	Grade I Grade II	3(21.4) 1(7.10)	5(13.2) 1(2.60)	0.778	0.678
Diarrhea	Grade I	4(28.6)	2(5.30)	FE 5.44	**0.038***
Bloating	Grade I	3(21.4)	2(5.30)	FE 3.07	0.114
Dizziness	Grade I	3(21.4)	2(5.30)	FE 3.07	0.114
Anemia	Grade I	2(14.3)	2(5.30)	FE 0.766	0.381
Myalgia	Grade I Grade II	4(28.6) 0(0.00)	7(18.4) 1(2.60)	0.942	0.624

Metformin was a safe drug easily administrated with minimal toxicity profile among the trial arm; 23 patients out of 66 had developed toxicities ranging from grade I to II, where grade 3 or 4 adverse effects did not occur during the period of treatment. The addition of metformin did not result in any development of unexpected adverse events or discontinuation of treatment.

GIT toxicity in the form of (nausea and anorexia) was the commonest type of toxicity affecting patients followed by dizziness.

Median PFS for the trial arm was 39 months (ranged between 35.9 - 43.7) and for the control arm was 30 months (ranged between 25.8 - 35.5) with a P-value of 0.005 **(Figure 1).**

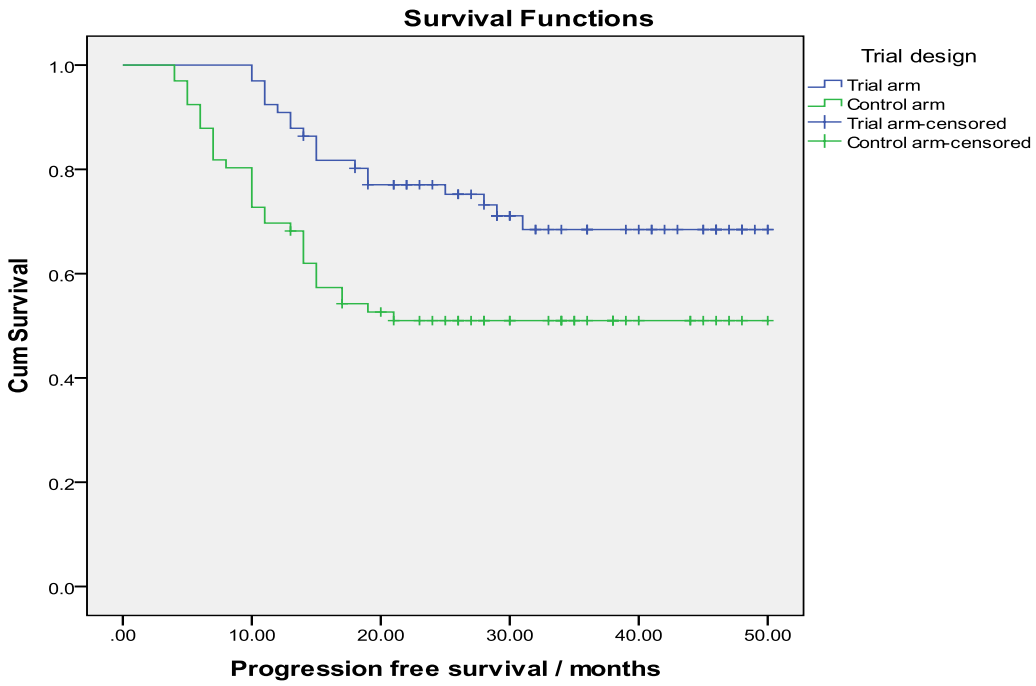

Figure (1): Kaplan-Meier curve shows mean PFS for both study groups It was 39 months for the trial arm (95% CI, 35.9-43.7) and 30 months for the control arm (95% CI, 25.8-35.5); (*P = 0.005).

We found that the presence of visceral metastasis (p=0.018) and PSA level (>2.75) after 6 months of starting treatment (p=0.002) were the most independent factors affecting patient PFS. By comparing both studied groups, regarding PFS and different clinicopathological features there was a statistically significant difference in disease volume (p=0.003), site of metastasis(p=0.001), different types of visceral metastasis (p=0.001), and presence of bone metastasis (p=0.001). **(Figure 2).**

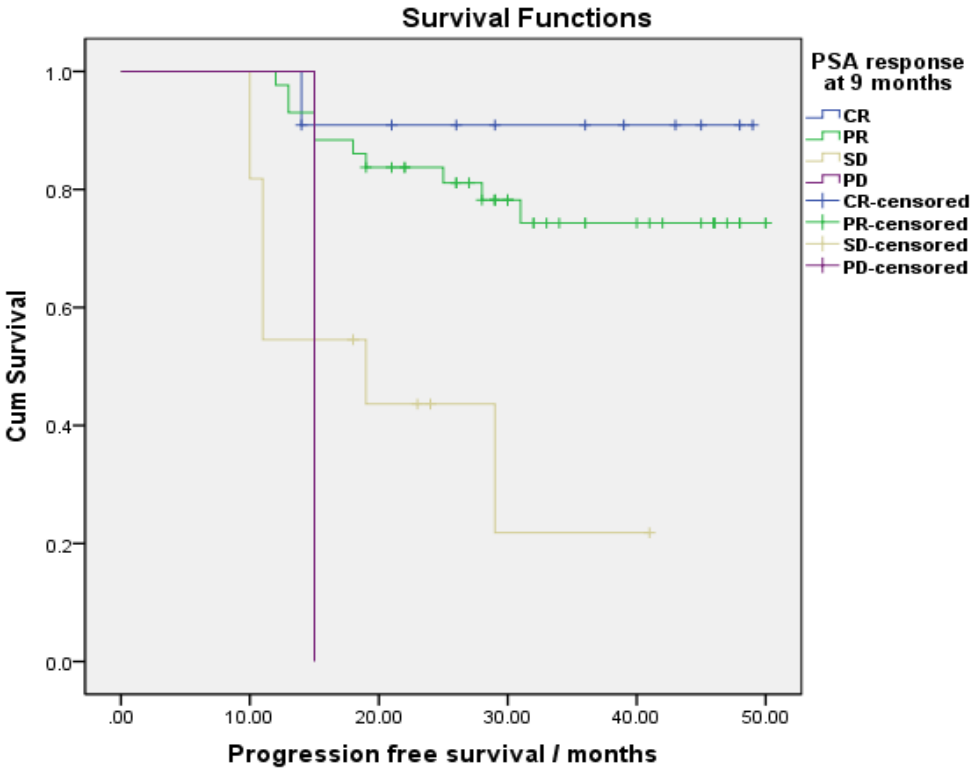

Figure (2): Kaplan-Meier curve shows the impact of PSA response at 9 months of treatment on PFS of prostate cancer patients among trial arm. Mean PFS of patients who had PD by PSA response criteria at 9 months of starting treatment were 15 months (95%CI, 15.0 -15.0) and were 45 months for those who had CR (95%CI, 39.8 –51.7) (*P=0.001).

The factors associated with significant shorter OS in the trial arm according to the present study were patients who had visceral metastasis (P=0.001), extra-regional lymph node metastasis (P=0.001), and median PSA >2.75ng/ml after 6 months of starting treatment(P=0.014) Median OS for the trial arm was 43 months (ranged between 40.4-46.2) and for the control arm was 35 months (ranged between 32.1 - 39.5) with a P-value of 0.00 (Figure 3)**.**

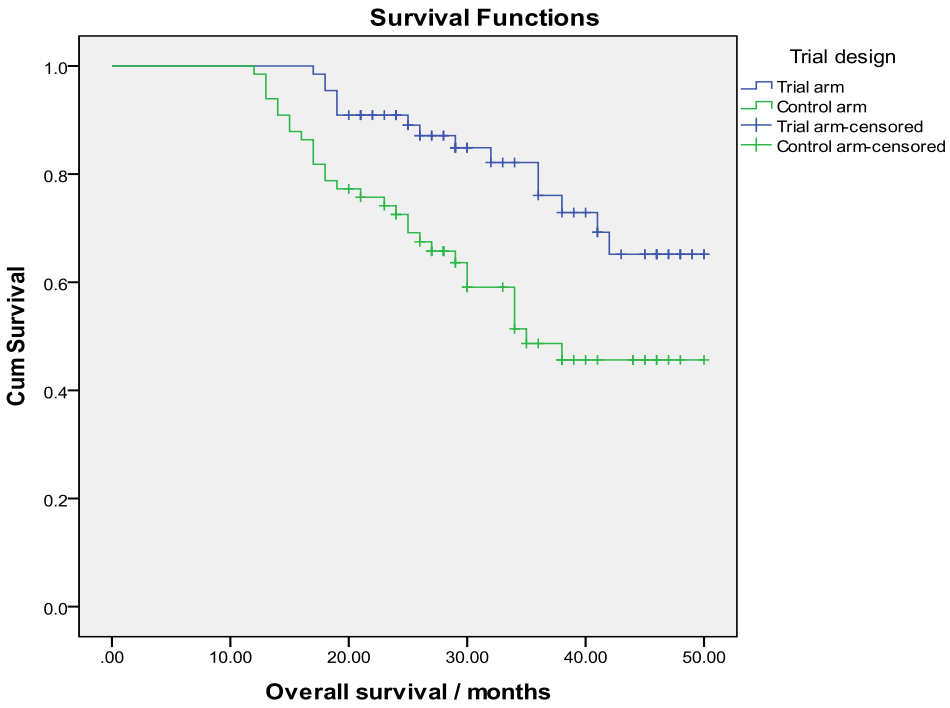

Figure (3): Kaplan-Meier curve shows mean OS for both study groups. It was 43 months for the trial arm (95% CI, 40.4-46.2) and 35 months for the control arm (95% CI, 32.1 - 39.5); (*P = 0.003).

Quality of life:

The pretreatment assessment of the quality of life by using Functional assessment of cancer therapy prostate (FACT-P) version: 4 was comparable among both study groups.

There was an improvement in the quality-of-life assessment during follow up period of the study in the trial arm compared to the control arm which showed a higher score during summation of all 5 concerns to obtain the total quality of life and it was statistically significant with (p =0.001) **(Table 4).**

Table (4): Quality of life before and after treatment among the studied groups (N = 132)

Quality of life	Studied groups		Mann Whitney test	P-value
	Group I Trial arm (N=66)	Group II Control arm (N=66)		
	Mean ±SD	Mean ±SD		
Physical wellbeing				
Baseline	4.60±4.16	3.45±2.06	1.01	0.310
Post-treatment	5.27±2.15	3.46±3.24	5.45	**0.001****
Follow up	6.87±3.32	2.89±3.03	6.69	**0.001****
Social family wellbeing				
Baseline	23.1±3.58	24.1±2.43	1.43	0.152
Post-treatment	24.1±2.55	22.2±2.81	3.95	**0.001****
Follow up	25.1±2.47	20.6±3.48	7.23	**0.001****
Emotional wellbeing				
Baseline	5.22±2.93	4.46±2.17	1.44	0.150
Post-treatment	5.98±2.55	4.33±2.24	4.44	**0.001****
Follow up	7.45±3.25	3.74±2.06	7.02	**0.001****
Functional wellbeing				
Baseline	22.7±3.34	23.6±1.86	1.26	0.207
Post-treatment	23.8±2.25	22.5±2.33	3.43	**0.001****
Follow up	24.1±3.28	21.6±3.02	5.00	**0.001****
Additional concern				
Baseline	30.3±7.20	30.2±5.00	0.947	0.344
Post-treatment	31.9±3.78	26.3±7.77	4.00	**0.001****
Follow up	33.7±3.99	23.8±7.70	7.09	**0.001****
Total quality				
Baseline	86.0±8.64	85.8±6.26	0.404	0.687
Post-treatment	87.9±5.39	82.0±8.12	3.89	**0.001****

Follow up	90.3±6.28	79.7±8.99	6.60	**0.001****

**High significant

DISCUSSION

Androgen deprivation therapy (ADT) is the mainstay and universally accepted first line of treatment in advanced and metastatic cancer prostate [7].

The role of metformin in the management of prostate cancer was investigated in many retrospectives and prospective trials both for metastatic and non-metastatic cases and discussed in systematic reviews evaluating metformin as adjuvant therapy in novel drug combinations in various disease settings [8].

In our trial, we combined metformin with combined ADT, based on what has been reported in the literature that adding metformin to combined ADT significantly reduced prostate cancer cell growth, which might improve prostate-cancer-specific survival [9]. In addition to the study conducted by **Richards *et al.*[10],** that observed an improvement in oncological outcome when metformin was combined with ADT in prostate cancer patients. Most included patients in our study had bone metastasis at the presentation this agrees with **Bader *et al.* [10], and Rothermundt *et al.* [12],** this is expected as bone metastases are the most common site of metastasis in advanced prostate cancer.

Pretreatment median PSA in our study arms was comparable to that found by **Bader *et al.* [10], and Alghandour *et al.* [13],** while it was considerably higher than in **Zhu *et al.* [14], and Seo *et al.* [15],** as our included patients had high tumor burden due to late presentation. The results in the present study showed that pretreatment median BMI was comparable to that reported by **Zhu *et al.* [14], Bader *et al.* [10], and with Rhee *et al.* [16]** study.

On the other hand, it seemed lower than that reported by **Rothermundt *et al.* [12]** the increase in median BMI in this study explained by patients who already had CRPC; in which obesity was considered a side effect of ADT. In comparison to the control group, metformin treatment led to a significant decline in weight, BMI, and random blood glucose levels towards the end of the study. These findings are in keeping with **Nobes *et al.* [17]** which showed that localized PCa patients treated with ADT and adjuvant metformin had a more favorable metabolic profile.

The incidence of skeletal-related events in our study is much higher than that reported by **Richards *et al.* [10],** this is due to the delayed presentation of our cases, and most of them presented by bone metastasis which goes with a high Gleason score (8-10) at baseline.

As expected, castration therapy dramatically reduced PSA levels in both study groups favoring metformin arm, especially the levels at 6 and 9 months, similar results were achieved in **Zhu *et al.* [14],** in which reduction in PAS levels was statistically significant after 6 months of initiating treatment. Similarly, **Rothermundt *et al.* [12],** found that metformin was shown to decrease PSA and prolong PSA doubling time CRPC patients.

On the contrary, **Rhee *et al.* [16]** found no statistically significant changes in PSA level or PSA-velocity between two groups during the follow-up, this could be explained by differences in study design in which randomization started after 12 weeks of ADT and a shorter duration of follow up for 54 weeks.

Regarding PSA response in both treatment arms, the difference was statistically significant at 9 months with p=0.004 favoring metformin group denoting need of longer duration of follow up for better effect on PSA response; similarly, **Richards *et al.* [10]** showed that subset analysis of patients with PSA greater than 20 ng/ml and at higher risk for metastatic disease in which ADT is typically initiated for hormone-sensitive PCa; confirmed the overall and cancer-specific survival advantage to being on metformin.

Controversial results achieved by **Alghandour *et al.* [13],** Adding metformin to the standard treatment in locally advanced and metastatic PCa patients did not have a significant effect on early or late decline in PSA levels (P-value = 0.5); this difference can be explained by trial having a heterogeneous population and heterogenous interventions for prostate cancer as they included patients with stage IIIA, IIIB, and MPC.

Regarding adverse effects in the current study, the trial arm showed 21.2% (n= 14/66) had toxicity related to treatment compared to 57.6% (n =38/66) in the control arm; with a better toxicity profile compared to the control arm in the occurrence of hot flashes, weight gain and development of edema except for nausea and diarrhea that were common in the metformin group. The treatment with metformin did not result in any cases of hypoglycemia or the development of unexpected adverse events.

The main adverse effect of metformin is an increased rate of nausea and diarrhea which were reflected in the trial. Regarding nausea about 28.6% of patients on metformin plus ADT reported grade 1 nausea and 14.3% of patients reported grade 2 compared to 7.90% of patients on ADT alone reported grade 1 and 2.60% of patients reported grade 2 respectively with (p-value 0.30); similar results by **Rothermundt *et al.* [12]** in which 16% of included patients had devolved grade 1&2 nausea and by **Rhee *et al.* [16]** in which nausea account for 2.6%compared to 0%in both trial arms respectively.

Regarding diarrhea about 28.6% of the patients on metformin plus ADT reported grade 1diarrhea compared with 5.3% of patients on ADT alone in the control arm (p-value 0.032); this is consistent with the result of a study conducted by **Rhee *et al.* [16]** in which diarrhea account for 6.5%compared to 0%in both trial arms respectively, **Rothermundt *et al.* [12]** detected 23% of included patients had diarrhea, **Alghandour *et***

al. **[13],** metformin did not show significant adverse events except self-limited diarrhea in three patients 4.8% (P-value 0.08).

Hot flashes were common in the control arm; 23.7%(n=9/66) had developed grade 2 toxicity compared to 7.1%(n=1/66) in the trial arm; this agrees with **Rhee *et al.*** **[16]** study in which occurrence of hot flashes represent 10.4% and 9.1% in both study groups, respectively.

50% of patients in the control arm (n=19/38) developed grade 1 weight gain which reflected on elevated median BMI at the end of follow-up (28.1in the control arm versus 23 in the trial arm).

In our trial with a median follow-up of 36 months, we reported that metformin prolonged the PFS by 9 months compared to the control arm (39 vs. 30 months; P = 0.005); this finding was in agreement with what was reported in A randomized controlled trial demonstrated that combining metformin to ADT increased castration-resistant prostate cancer-free survival by 9 months compared to ADT alone (29 vs. 20 months; P = 0,01) **[13]**.

A meta-analysis suggested that the addition of metformin to ADT improved PCa-specific survival and overall survival, which could suggest greater sensitivity to metformin in the hormone-sensitive prostate cancer population **[18]** Metformin could potentiate the efficacy of ADT and extend the cell death effects of bicalutamide **[19].**

In our study, the univariate analysis for PFS in the metformin group showed that disease volume, site of metastasis, presence of visceral metastasis, PSA response at 9 months of treatment, and Radiological response at 9 months were identified factors to affect survival outcomes. Cox regression of progression-free survival revealed that presence of visceral metastasis and PSA response at 9 months were an independent predictor for it with a hazard ratio (4.06; 95% CI, 1.39 - 11.8; P=0.010) and (5.15; 95% CI, 2.15 -12.3; P =0.001) respectively.

Like our results, **Rhee *et al.*** **[16]** reported the positive impact of metformin administration on PFS. Also, **Taussky *et al.*** **[20],** found that patients who received metformin experienced a 50% reduction in PFS in the localized prostate cancer setting.

Like **Xiao *et al.*** **[21],** extracted data from a meta-analysis of 177,490 individuals from 13 cohort studies, five of which investigated recurrence-free survival (RFS) as the endpoint. Random effects modeling revealed metformin use to be significantly associated with improved RFS (HR: 0.74; 95% CI: 0.58–0.95).

Not all meta-analyses have demonstrated a positive association between the use of metformin and improved RFS following primary treatment. **Hwang *et al.*** **[22]** used five RFS studies and showed no statistical significance for outcomes this may be due to the limited number of included studies and small sample size**.**

In our study overall survival in univariate analysis for the metformin group was significantly affected by sit of metastasis, presence of visceral metastasis, and PSA response at 9 months of treatment. Cox regression of overall survival revealed that the presence of visceral metastasis was an independent predictor for it with a hazard ratio (P=0.012).

In metanalysis by **Stopsack *et al.*** **[23],** utilized data from 9186 patients included in nine retrospective cohort studies; the result of analyzing six studies that investigated OS as an endpoint, metformin was associated with a superior OS outcome (HR: 0.88; 95% CI: 0.86–0.90).

Similar results on the effect of metformin on PFS& OS obtained by recent meta-analysis included data from 660,795 patients in 30 cohort studies this study revealed that metformin treatment improves OS, CSS and RFS in PC (HR = 0.72, 95% CI: 0.59–0.88, P = 0.001; HR = 0.78, 95% CI: 0.64–0.94, P = 0.009; and HR = 0.60, 95% CI: 0.42–0.87 P =0.006, respectively) compared with non-metformin treatment **[18]**.

Moreover, metformin was beneficial in the subgroup of patients who received ADT (HR: 0.77; 95% CI: 0.74–0.81), suggesting that metformin exhibited therapeutic benefits that outweighed the detrimental effect of ADT on metabolic syndrome **[18]**.

The proportion of patients documented to have died of PCa was lowest in the trial arm at 22.7% and 45.5% in the control arm p-value 0.006; this agrees with the result in **Richards *et al.*** **[10]** which documented the proportion of patients who have died of PCa was lowest in the metformin group at 9.3% p value< 0.001, this explains the effect of metformin in reducing mortality and improve CSS when added to the treatment of PCa**.**

Another important issue with ADT is the numerous associated side-effects, particularly with prolonged use. Since patients continue LHRH after disease progression (with additional agents added), many people remain on treatment for a decade or longer; metformin aims to mitigate some of the adverse effects of ADT which include adverse metabolic disturbance, cognitive decline, sexual dysfunction, hot flushes, physical deterioration, and fatigue **[24]**.

Metformin was tolerated and treatment-related side effects were minimal and easily manageable were grade 3 or 4 adverse effects did not occur during the period of treatment; this is like previous studies conducted by **Rothermundt *et al.*** **[12], Alghandour *et al.*** **[13], and Rhee *et al.*** **[16].**

There was an improvement in the quality-of-life assessment during the follow-up period in our study in the trial arm compared to the control arm, this suggests potential benefits of adding metformin to ADT in reducing adverse effects of treatment, prolongation of time to progression to CRPC, and better PFS & OS.

In the current study, we achieved promising results with the addition of metformin to the combined ADT in the improvement of both PFS and OS so as we

have limited resources being in Egypt one of the developing countries the newly approved lines of treatment (mHNPC) were not available and expensive to be feasible for all patients so, Metformin considered a good option for our patients as it is a familiar oral drug, cheap, will be tolerated with minimal related side effects and available in all places, compared to the newly approved agents like abiraterone, apalutamide, enzalutamide, or docetaxel.

Our current study has some limitations; we did not track body fat mass, nor did we measure insulin level or C-peptide level in the study participants. We believe that all these tests could have added great value in examining the ability of metformin to reduce the metabolic complications of ADT.

Due to controversial results of the effect of metformin in prostate cancer. The multi-arms, multistage and randomized STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer; Evaluation of Drug Efficacy and ClinicalTrials.gov NCT00268476) that clinical trial is currently recruiting patients in a metformin plus ADT arm (arm K) to assess the effect safety profile of metformin combined with ADT in advanced cancer prostate patients and to assess whether metformin can improve all-cause survival. The patients will be allowed ADT +/- prostate radiotherapy +/- docetaxel + metformin and compared with other 10 arms of the trial and randomized, prospective phase 3 PRIME (Metformin in Patients Initiating ADT as Prevention and Intervention of Metabolic Syndrome, Clinical- Trials.gov NCT03031821) clinical trial that underway to assess the number of patients those develop the metabolic syndrome [(25)]

CONCLUSION

Metformin should be considered as an effective agent to be used in combination with standard treatments for PCa, the present study showed that Metformin use was associated with improved PFS and OS.

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