A retrospective review of the effect of metformin in metastatic prostate cancer

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INTRODUCTION

- Prostate cancer is the third most common cancer with 31,620 estimated deaths and 174,650 estimated new cases in the United States in 2019.[1]
- Current treatments of metastatic prostate cancer are mainly hormone therapy and chemotherapy. However these treatments have short durations of response and associated toxicities.
- Metformin, a benign and common medication used for diabetes, was reported to have antineoplastic effects by shifting cancer cells from an anabolic to catabolic state.[2]
- Metformin activates AMP-activated protein kinase (AMPK), which decreases insulin secretion, inhibits gluconeogenesis and energy consuming processes, and stimulate ATP-generating processes.[3]
- Currently, there are several mixed reports regarding the anticancer potential of metformin in reducing the incidence of certain cancers.

OBJECTIVE

- In this study, we aim to investigate the effect of metformin on metastatic prostate cancer.

METHODS

- Our institutional review board approved this retrospective review of metastatic prostate cancer patients between 2014 and the end of 2018 at the Monter Cancer Center of Northwell Health.
- Patients were stratified as shown in Figure 1.
- **Outcomes**: 6-month PSA response, overall survival (OS), and progression free survival (PFS) were evaluated based on PCWG3 and RECIST criteria.
- Fisher's exact test was used to compare groups with respect to the 6-month PSA response rates, the Kaplan-Meier method to estimate survival and PFS stratified by group using the log-rank test, and the Cox regression was carried out.
- Results were statistically significant at the p<0.05 level of significance. All analyses were performed using SAS version 9.4.

RESULTS

Figure 1. Patient stratification, n (%)

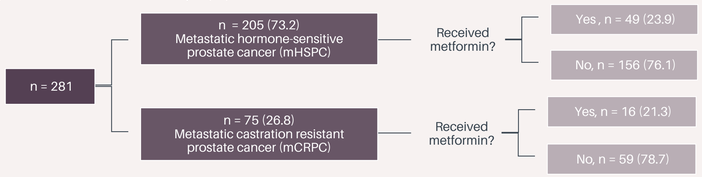


Table 1. Demographics and characteristics

BASELINE CHARACTERISTICS , mean (SD)	
Age, years	70.3 (9.95)
Height, cm	174.4 (7.49)
Weight, kg	86.15 (17.8)
BMI	28.32 (5.17)
RACE, n (%)	
White	143 (50.89)
Black	56 (19.93)
Asian	14 (4.98)
More than one race	1 (0.36)
Not reported	67 (23.84)
ECOG PERFORMANCE STATUS, n (%)	
0	116 (42.7)
1	83 (30.5)
2	39 (14.3)
3	28 (10.3)
4	6 (2.2)

Table 2. Risk of progression and PFS

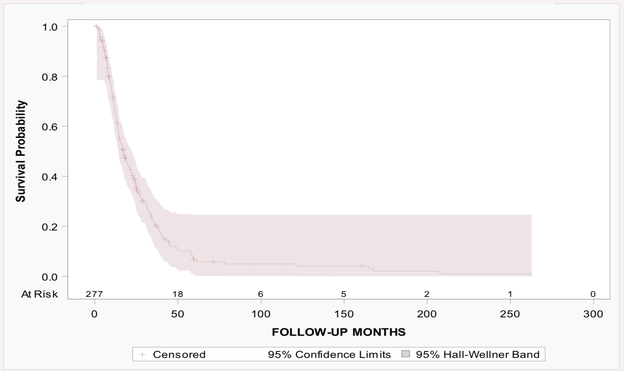
	mHSPC	mCRPC	p-value
HR of progression	0.893 (0.616 - 1.294)	2.648 (1.400 - 5.011)	-
PFS, months	17.9	13.6	< 0.01

Table 3. Overall responses

	METFORMIN	NO METFORMIN	p-value	ALL
PFS, months	16.6	17.3	< 0.88	17
OS, months	148.5	69.4	< 0.02	81.5
6-month PSA response	70.4%	72.9%	< 0.73	72.4%
• mHSPC	80.3%	79.8%	< 1.0	79.1%
• mCRPC	38.5%	54.4%	0.36	50.9%
HR of death	0.58 (0.33 to 1.02)	-	< 0.06	-

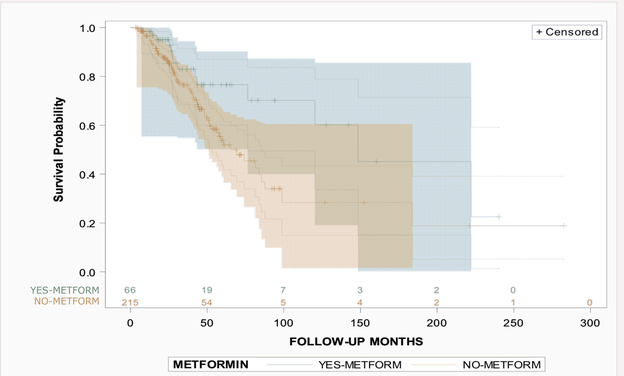
- Within the mHSPC group, metformin users had a lower risk of progression (risk reduction of 11% but not statistically significant) relative to non-users.
- Within the mCRPC group, metformin users had a significantly higher risk of progression relative to non-users (HR=2.65; 95% CI: 1.4 to 5.0). However, there was a significant difference in PFS between mHSPC and mCRPC (17.9 vs. 13.6; p<0.01).
- There was no significant difference in PFS between groups with and without metformin (16.6 vs. 17.3; p<0.88).
- There was no significant difference between metformin groups with respect to PSA response at 6-months (p<0.73). Within the mHSPC group, the 6-month PSA response rates according to metformin use (yes vs. no) were 80.5% (33/41) and 79.8% (115/146) respectively, p<1.0; within the mCRPC group, the 6-month PSA response rates according to metformin use were 38.5% (5/13) and 54.4% (25/46), p=0.36.
- Among those with a recorded 6-month PSA response, 70.4% (38/54) had a response in the metformin group and 72.9% (140/192) had a response in the non-metformin group.

Figure 3. Kaplan-Meier Estimate of Median Progression Free Survival



- Overall median progression-free survival was estimated to be 17 months.

Figure 4. Kaplan-Meier Estimate of Median Overall Survival



- Median overall survival was estimated to be 81.5 months. There was a significant difference in survival time between groups with and without metformin (148.5 vs. 69.4; p<0.02).

DISCUSSION

- The standard of care for metastatic prostate cancer remains limited and we currently do not have a biomarker to predict the response of treatment among special patients.
- Metformin's potential antineoplastic actions are of high interest and is also being added as an arm in the phase III, prospective, randomized STAMPEDE trial to be studied for its effects in improving all-cause survival.[4]
- A recent study also provides direct evidence of PTEN loss as a potential biomarker to predict metformin's effects in the clinical outcomes of prostate cancer patients.[5]
- **Limitations**: This study was retrospective in nature. Additionally, metformin status could be specified with respect to timing and duration.

CONCLUSION

- No significant differences were found in 6-month PSA response or PFS; however, there was a significant difference in OS amongst patient who were in the metformin group and those who were not.
- This study provides further evidence and reasoning to conduct prospective studies involving metformin in metastatic prostate cancer.

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