Impact of Metabolic Diseases and Drugs on Prostate Cancer Patients Receiving Androgen Deprivation Therapy

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Introduction

- Metabolic diseases and drugs are among the variables influencing on the outcome of prostate cancer (PCa) patients receiving androgen deprivation therapy (ADT).
- We reviewed articles related to metabolic diseases and drugs and listed them as Table 1.
- Established risk factors for them are still limited and not conclusive.
- The aim of our study was to evaluated the effect of metabolic diseases and drugs on the time to development of PSA progression (castration-resistant disease) in patients receiving ADT.
- Table 1. Metabolic diseases and drugs on the prognosis of PCa patients with ADT

Environmental factor	Authors	Number of cases	Treatment modality	Primary endpoint	Outcome
Smoking	Oefelein MG et al., J Urol. (2004)	222 advanced PCa	ADT	Time to CRPC, OS	Worse outcome in time to CRPC and OS.
Diabetes mellitus	Hu MB et al. Int J Clin Oncol. (2018)	435 PCa (72 with concurrent diabetes)	Bilateral orchiectomy	OS	No significant difference in OS.
	Shevach J et al. Front Oncol. (2015)	148 advanced PCa (35 with concurrent diabetes)	ADT	Time to CRPC, OS	No difference in time to CRPC; Worse OS in older patients (> 75 years old).
	Smith MR et al. J Clin Oncol. (2008)	1554 all stage PCa	Radiotherapy with ADT	OS, prostate cancer specific mortality	Worse outcome in OS, but not prostate cancer mortality.
Hypertension	Shiota M et al. Front Oncol. (2018)	182 PCa (with 89 concurrent hypertension)	ADT	Time to CRPC, OS	Better outcome in time to CRPC and OS.
Obesity	Hu MB et al. Int J Clin Oncol. (2018)	435 PCa (126 with concurrent obesity)	Bilateral orchiectomy	OS	Better OS in younger patients (age ≤ 65)
	Christopher J et al. BJU Int. (2012)	287 PCa	RP + continuous ADT	Time to CRPC, prostate cancer specific mortality	A trend of worse outcome in time to CRPC and prostate cancer specific mortality
Hyperlipidemia	Jong Chul Jeon et al. World J Mens Health. (2016)	154 PCa	ADT	Time to CRPC	Worse outcome in time to CRPC in patients with bone metastasis
Statin use	Harshman LC et al. JAMA Oncol. (2015)	926 (283 with statin use)	ADT	Time to progression	Better outcome in time to progression
Aspirin use	L Yang et al. Lancet. (2016)	80 (22 with aspirin use)	ADT	CRPC	No significantly difference.
Metabolic syndrome	J. Flanagan et al. Ann Oncol. (2011)	82 (40 wit metabolic syndrome)	ADT	Time to CRPC, OS	Worse outcome in time to CRPC.

Materials and Methods

- We retrospectively enrolled prostate cancer patients seen from 1997 to 2005 in the clinics of Brigham and Women's Hospital and Dana-Farber Cancer Institute.
- The inclusion criteria was PCa patients receiving long term ADT (at least 12 months) , either due to biochemical relapse after local therapy or metastasis.
- We collected adequate information to evaluate for the presence of diabetes, hypertension, obesity, statin use, aspirin use, metformin use, hyperlipidemia, and metabolic syndrome at the initiation of ADT.
- Time to castration-resistant prostate cancer (CRPC) was defined as duration between ADT start and sequence of rising prostate specific antigen (PSA) values at a minimum of 1-week intervals, and 1.0 ng/ml is the minimal starting PSA level.
- Time to CRPC was treated as time-to-event data in the analysis.

Results

- Four hundred and twenty-two patients treated with ADT were identified and the median age was 62 years old. (Table 2)
- 365 (86.5%) prostate cancer patients experienced CRPC after ADT and the median time from ADT initiation to CRPC was 19.6 months. (Table 2)
- 304 (72%) patients died and the median time from ADT initiation to CRPC was 68.6 months. (Table 2)

Table 2. Clinical characteristics of the study population

Characteristic	
Number of Patients	422
Age at diagnosis	
Median, years (IQR)	62 (56-67)
Race, n (%)	
White	358 (84.8)
Black	16 (3.8)
Unknown	48 (11.4)
Biopsy Gleason score at diagnosis, n (%)	
≤7	173 (41.0)
>7	210 (49.8)
Unknown	39 (9.2)
Clinical M stage at diagnosis, n (%)	
M0	238 (56.4)
M1	166 (39.3)
Unknown	18 (3.7)
PSA at ADT initiation, ng/mL	
Median (IQR)	26.4 (9.0-104.7)
PSA nadir, ng/mL	
Median (IQR)	0.16 (0.01-1.20)
Time to PSA nadir, mo	
Median (IQR)	7.8 (4.0-12.8)
Median time from ADT initiation to CRPC, mo (95% CI)	19.6 (17.7-22.5)
Median time from ADT initiation to all cause mortality, mo (95% CI)	68.6 (60.2-76.9)
Treatment modality, n (%)	
ADT as primary treatment	199 (47.2)
ADT for post RP PSA failure	135 (32.0)
ADT for post RT PSA failure	83 (19.7)
Others	5 (1.1)
Environmental factors, n (%)	
Smoking (Active)	69 (16.4)
Diabetes Mellitus	48 (11.4)
Hypertension	220 (52.1)
Obesity (BMI>30)	144 (34.1)
Hyperlipidemia	223 (52.8)
Statin user	141 (33.4)
Aspirin user	125 (29.6)
Metformin user	42 (10.0)
Metabolic syndrome	179 (42.4)

Abbreviations: ADT, androgen deprivation therapy; BMI, Body mass index; CI, confidence interval; CRPC, Castration-resistant prostate cancer; IQR, interquartile range; PSA, prostate-specific antigen; RP, radical prostatectomy; RT: radiotherapy.

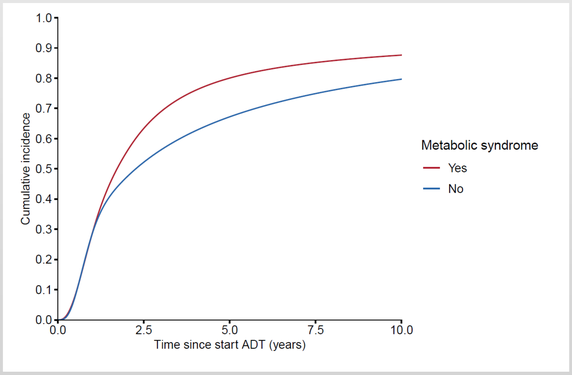
- Metabolic syndrome was most associated with time to CRPC (hazard ratio: 1.36, confidence interval: 1.04-1.77) after controlling for confounders. (Table 3, Figure 1)
- Table 3. Hazard ratio for CRPC by metabolic disease or medication

Variable	Label	HR_unadj	HR_adj1	HR_adj2
Smoking (ever)	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.02 (0.82-1.26)	0.99 (0.79-1.24)	1.05 (0.82-1.33)
Diabetes mellitus	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.24 (0.90-1.71)	1.27 (0.89-1.82)	1.22 (0.83-1.79)
Hypertension	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.16 (0.94-1.42)	1.27 (1.01-1.59)	1.27 (1.00-1.61)
Obesity	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.09 (0.88-1.36)	1.05 (0.83-1.33)	1.04 (0.80-1.34)
Hyperlipidemia	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	0.85 (0.69-1.04)	0.85 (0.68-1.06)	0.89 (0.70-1.12)
Metabolic syndrome	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.44 (1.13-1.83)	1.38 (1.07-1.78)	1.36 (1.04-1.77)
Statins	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	0.74 (0.59-0.93)	0.75 (0.58-0.95)	0.79 (0.61-1.02)
Aspirin	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	0.79 (0.63-0.99)	0.78 (0.61-1.00)	0.80 (0.61-1.05)
Metformin	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.05 (0.69-1.60)	1.10 (0.69-1.76)	1.08 (0.66-1.75)

Adjustment 1: age at ADT initiation, year of ADT initiation, and race

Adjustment 2: age at ADT initiation, year of ADT initiation, race, M1, Gleason 7+, PSA at ADT initiation, primary treatment

- Figure 1. Standardized cumulative incidence of CRPC (controlling for confounding)



- No individual components of metabolic syndrome was independently associated with time to CRPC. (Table 4)
- Table 4: Hazard ratio for CRPC by individual components of metabolic disease.

Variable	Label	HR_adj1	HR_adj2
BP135_80	No	1 (Ref.)	1 (Ref.)
	Yes	1.08 (0.84-1.40)	0.99 (0.70-1.40)
BMI30	No	1 (Ref.)	1 (Ref.)
	Yes	1.02 (0.80-1.32)	1.08 (0.77-1.49)
HDL40	No	1 (Ref.)	1 (Ref.)
	Yes	1.10 (0.82-1.47)	0.75 (0.44-1.27)
TG150	No	1 (Ref.)	1 (Ref.)
	Yes	1.22 (0.91-1.63)	1.33 (0.78-2.27)
Glucose110	No	1 (Ref.)	1 (Ref.)
	Yes	1.35 (0.99-1.83)	1.55 (1.07-2.25)

Adjustment 1: age at ADT initiation, year of ADT initiation, race, M1, Gleason 7+, PSA at ADT initiation, primary treatment

Adjustment 2: all of above + the other components

- Interestingly, comparing the metabolic syndrome patients with statin use and without statin use, the cumulative incidence of CRPC was higher in the group of patients without statin use. (Table 5, Figure 2)
- Table 5. Hazard ratio for CRPC by combinations of metabolic disease and statins/aspirin/metformin.

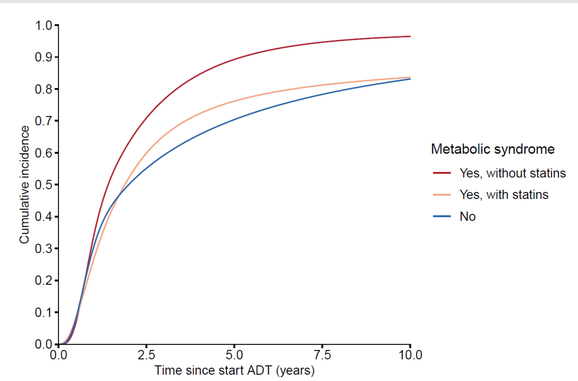
Variable	Label	HR_ref1	HR_ref2
Metabolic syndrome	No	1 (Ref.)	0.60 (0.41-0.87)
	Yes, without statins	1.67 (1.14-2.43)	1 (Ref.)
	Yes, with statins	1.09 (0.81-1.47)	0.66 (0.45-0.96)
	Only statins	0.44 (0.22-0.88)	0.27 (0.13-0.56)
Metabolic syndrome	No	1 (Ref.)	0.77 (0.55-1.07)
	Yes, without aspirin	1.30 (0.94-1.80)	1 (Ref.)
	Yes, with aspirin	1.19 (0.84-1.70)	0.92 (0.64-1.32)
	Only aspirin	0.61 (0.35-1.07)	0.47 (0.26-0.83)
Metabolic syndrome	No	1 (Ref.)	0.73 (0.55-0.96)
	Yes, without metformin	1.37 (1.04-1.81)	1 (Ref.)
	Yes, with metformin	1.28 (0.76-2.15)	0.93 (0.55-1.57)
	Only metformin	0.99 (0.98-1.01)	0.99 (0.98-1.01)
Metabolic syndrome	No	1 (Ref.)	0.66 (0.42-1.04)
	Yes, without medication	1.51 (0.97-2.38)	1 (Ref.)
	Yes, with medication	1.14 (0.84-1.55)	0.75 (0.48-1.17)
	Only medication	0.62 (0.38-1.02)	0.41 (0.23-0.75)

Adjustment: age at ADT initiation, year of ADT initiation, race, M1, Gleason 7+, PSA at ADT initiation, primary treatment

Ref1: "No" is the reference group

Ref2: "Yes, without ..." is the reference group

- Figure 2. Standardized cumulative incidence of CRPC (controlling for confounding)



Conclusion

- Our data suggest that metabolic syndrome is a risk factor for earlier development of CRPC.
- Patients with metabolic syndrome and statin use had longer time to progression to CRPC than patients without statin use.
- This study highlights the need as well as provides the support for future prospective investigation to better characterize the association of metabolic syndrome and statin user with clinical outcomes in prostate cancer.

Acknowledgements

- The data of this project was provided from the Gelb Center Committee.
- Special thanks to Anna Plym, John A Steinharter, Grace K Shaw, and Victoria Wang.