Decreased testosterone recovery after androgen deprivation therapy for prostate cancer

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Introduction: *Androgen deprivation therapy (ADT) is often used in the treatment of prostate cancer. Specific factors affecting testosterone recovery after cessation of ADT have not been well-characterized in existing literature.*

Materials and methods: *We retrospectively reviewed patients at our institution who received ADT between 1999 and 2018. Patients with at least one course of ADT and subsequent testosterone level within 12 months of cessation of ADT were included. Patients received at least one of the following four agents: leuprolide, goserelin, triptorelin, and degarelix. Cox regression models were utilized to estimate the effect of patient and treatment characteristics on time to testosterone recovery (≥ 240 ng/dL) after ADT cessation. Patients without testosterone recovery were censored at last testosterone evaluation. To account for the possible dependency between multiple ADT courses within a patient, we used a robust sandwich variance estimate.*

Results: *Severty-six patients were included. Mean age was 64 +/- 8 years. Median duration of ADT was 15 months, with a median time to recovery of 19 months. On univariable analysis, age and duration of ADT were significant; a trend towards significance was noted for hypertension, diabetes, peripheral vascular disease, goserelin and bicalutamide. Patient age, duration of ADT, and treatment with the agent goserelin were significantly associated with prolonged hypogonadism on multivariable analysis ($p < 0.01$).*

Conclusions: *Increasing age and duration of ADT therapy are associated with decreased likelihood to recover normal testosterone levels after cessation of therapy. The use of the ADT agent goserelin was also associated with decreased testosterone recovery for unclear reasons.*

Key Words: androgen deprivation therapy, hypogonadism, prostate cancer, goserelin

Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer and is one of the leading causes of cancer death for men in the United States.[1] Androgen deprivation therapy (ADT) is currently a mainstay of treatment and has been shown to prolong the lives of men with prostate cancer.[2] However, ADT is also associated with numerous side effects, including hot flashes, erectile dysfunction, weight gain, loss of bone mineral density, and gynecomastia, all of which can significantly affect patient quality of life.[2,3] These side effects can be improved or eliminated if recovery to a normal testosterone level is achieved once ADT is stopped.[4]

Previous studies have reported varying rates of partial and total testosterone recovery after ADT cessation.[5-7] However, there is currently not a clear understanding of the specific factors affecting testosterone recovery. More insight into such factors would allow us to better counsel patients on the individual risk factors associated with failure of testosterone recovery after ADT discontinuation, and thus the anticipated duration of associated side effects. In this retrospective study, we sought to further characterize factors that affected testosterone recovery after discontinuation of ADT.

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Materials and methods

After Institutional Review Board approval (IRB ID #: 201901779), we conducted a retrospective chart review of patients at our institution who received ADT for the treatment of prostate cancer between January 1, 1999 and December 31, 2018. Records for 212 patients were initially screened. Patients with continuous treatment or patients lacking a subsequent testosterone measurement within 12 months of the last effective ADT treatment date were excluded from the study. Some patients received more than one course of ADT. Each course was treated and analyzed separately. Only those courses that had an associated testosterone value within 12 months of the course were included in the analysis. A total of 76 separate patients and 83 separate courses of ADT were included in the final analysis. We included patient demographics, lifestyle characteristics, medical co-morbidities, and ADT treatment characteristics in our data review.

Complete testosterone recovery was defined as a testosterone level ≥ 240 ng/dL after ADT cessation. Complete castration was defined as a testosterone level < 50 ng/dL. Supra-castration was defined as a testosterone value between these two ranges (≥ 50 ng/dL but < 240 ng/dL). The duration of ADT-use was counted from the time of the administration of the agent to the calculated withdrawal date of the agent. Because various agents have specific reaction times, this withdrawal timing differed to be either a 1, 3, or 6-month increment, depending on the specific agent administered.

Cox regression models were utilized to estimate the effect of patient and treatment characteristics on testosterone recovery-free survival. Time was calculated from the end of each ADT course to time of testosterone recovery. Patients who did not recover were censored at last testosterone evaluation. To account for the possible dependency between multiple ADT courses within a patient, a robust sandwich variance estimate was used. Estimated effects of predictors were reported as hazard ratios (HR) along with 95% confidence intervals. In our analysis, a HR less than 1 indicated decreased likelihood of testosterone recovery, whereas a HR greater than 1 indicated increased likelihood of testosterone recovery. All tests were two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

The median age was 62.50 years old (mean ± standard deviation [SD], 63.72 ± 8.39). Almost all patients in the cohort were Caucasian (71); other races represented in the cohort include African American (1), Asian (1),

TABLE 1. **Patient lifestyle**

Variable	Level	n = 76	%
Current or former smoker	No	28	36.8
	Yes	48	63.2
Alcohol use	No	37	51.4
	Yes	35	48.6
	Missing		4
Obstructive sleep apnea	No	66	86.8
	Yes	10	13.2
Peripheral vascular disease or coronary heart disease	No	57	75.0
	Yes	19	25.0
Hypertension	No	28	36.8
	Yes	48	63.2
Diabetes	No	58	76.3
	Yes	18	23.7
Chronic kidney disease	No	73	96.1
	Yes	3	3.9
Liver disease	No	75	98.7
	Yes	1	1.3

TABLE 2. **Patient health co-morbidities**

Variable	n	Missing	Min	Max	Median	Mean	Standard deviation
Age	76	0	50.00	85.00	62.50	63.72	8.39
Body mass index	76	0	19.24	48.69	29.54	30.13	5.88
Pack years	34	42	0.50	150.00	18.25	25.41	31.11
Drinks per week	35	41	1.00	100.00	2.00	7.14	16.93

Caucasian-Hispanic (2), and unspecified (1). Patient lifestyle and health co-morbidities are characterized in Table 1 and 2.

Forty-three (56.6%) patients received only one course of ADT, 22 patients (28.9%) underwent two courses, 7 (9.2%) patients underwent three courses, and 4 (5.2%) patients underwent four or more courses. The median duration of a course of ADT was 15.31 months (22.45 ± 25.70). The various ADT agents used were leuprolide (40.2% of courses), goserelin (24.4%), triptorelin (51.2%), degarelix (14.6%), and histrelin (1.2%). Additionally, in 55 (66.3%) of courses, Combined Androgen Blockade/Maximum Androgen Blockage (CAB/MAB) was used by adding the antiandrogen agent bicalutamide to the primary agent. Bicalutamide was never given as a monotherapy.

On univariable analysis, Table 3, increasing age (HR 0.93; CI 95%, 0.89-0.98, $p < 0.01$) and duration of ADT

TABLE 3. **Univariable analysis**

		Testosterone recovery-free survival			
Covariate	**Level**	**Hazard ratio**	**95% CI**		**p value**
Smoker	Yes	0.82	0.39	1.73	0.60
	No	Ref	-	-	-
Alcohol use	Yes	1.24	0.63	2.44	0.54
	No	Ref	-	-	-
Obstructive sleep apnea	Yes	0.67	0.24	1.90	0.45
	No	Ref	-	-	-
Peripheral vascular disease or coronary heart disease	Yes	0.50	0.24	1.06	0.07
	No	Ref		-	- -
Hypertension	Yes	0.52	0.27	1.00	0.05
	No	Ref	-	-	-
Diabetes	Yes	0.42	0.17	1.00	0.05
	No	Ref	-	-	-
Lupron/Eligard	Yes	0.68	0.34	1.35	0.27
	No	Ref	-	-	-
Goserelin/Zoladex	Yes	0.55	0.29	1.05	0.07
	No	Ref	-	-	-
Trelstar/Triptorelin	Yes	1.30	0.67	2.50	0.43
	No	Ref	-	-	-
Degarelix/Firmagon	Yes	0.62	0.16	2.37	0.49
	No	Ref	-	-	-
Bicalutamide	Yes	0.51	0.25	1.03	0.06
	No	Ref	-	-	-
Age	Units = 1	0.93	0.89	0.98	< .01
Body mass index	Units = 1	1.00	0.95	1.05	0.89
ADT duration (months)	Units = 1	0.97	0.95	0.99	< .01

TABLE 4. **Multivariable analysis**

		Testosterone recovery-free survival			
Covariate	**Level**	**Hazard ratio**	**95% CI**		**p value**
Goserelin	Yes	0.34	0.16	0.69	< .01
	No	Ref	-	-	-
Age	Units = 1	0.93	0.89	0.97	< .01
ADT duration (months)	Units = 1	0.97	0.95	0.99	< .01

(HR 0.97; CI, 95%, 0.95-0.99, p < 0.01) were significantly associated with decreased likelihood of testosterone recovery. Notably, ADT treatment courses which included the LHRH agonist goserelin (HR 0.55; CI 95%, 0.29-1.05, p = 0.07) or the anti-androgen adjunct agent bicalutamide (HR 0.51; CI 95%, 0.25-1.03, p = 0.06) trended toward decreased likelihood of testosterone recovery. The medical co-morbidities hypertension (HR 0.52; CI 95%, 0.27-1.00, p = 0.05), vascular disease or coronary heart disease (HR 0.50; CI 95%, 0.24-1.06, p = 0.07) and diabetes (HR 0.42; CI 95%, 0.17-1.00, p = 0.05) were also associated with a trend towards decreased likelihood of testosterone recovery, albeit not statistically significantly.

On multivariable analysis, Table 4, increasing age (HR 0.93; CI 95%, 0.89-0.97, p < 0.01) and increasing duration of ADT (HR 0.97; CI 95%, 0.95-0.99, p < 0.01) were significantly associated with decreased recovery of testosterone. ADT courses including goserelin were associated with a 66% decreased likelihood of testosterone recovery (p < 0.01).

Discussion

Increasing age and duration of continuous ADT were associated with decreased likelihood of recovery in our study. This is consistent with results from previous studies. A prospective study by Yoon et al[6] demonstrated that younger age was significantly associated with faster return to supracastrate testosterone levels, and younger age and shorter duration of therapy were significant for faster return to normal testosterone levels. Another retrospective study showed significant difference in rates of testosterone recovery between patients receiving ≤ 18 months of ADT versus patients who received treatment > 18 months.[7]

Our study also noted a trend toward significance for various other factors, including hypertension, vascular disease or coronary artery disease, and diabetes mellitus. Limited data suggest that there may be a significant association between hypertension and diabetes. Nam and associates[7] noted a significant association between hypertension and decreased testosterone recovery to both a supracastrate and out-of-hypogonadism level (univariate, p = 0.028 and p = 0.037). This same retrospective study also reported an association between diabetes and decreased recovery to an out-of-hypogonadism testosterone level (univariate, p = 0.021).

While one of only a few studies to assess the effects of individual LHRH agonists, this is to our knowledge the first study to show a significant effect of an individual ADT agent (Goserelin/Zoladex) on testosterone recovery. Tsumura and colleagues[8] previously compared the effect of LHRH agonists goserelin and leuprorelin on testosterone recovery in patients with concurrent prostate brachytherapy. Univariate analysis suggested that there was no significant difference between the use of the two agents (HR 0.973; CI 95%, 0.579-1.6735, p = 0.917), although patients in the study were assessed after long term (≥ 36 months) duration of ADT. Our results conversely showed a trend toward significance in univariate analysis and a significant difference in multivariate analysis when comparing goserelin to the other LHRH agonist agents. The reason for this significant difference is unclear. It is possible that, rather than being a specific drug effect, the association has to do with the dosage or duration of action. Further investigation is necessary to fully explore this association.

Interestingly, the new oral GNRH antagonist, relugolix, is thought to have drastically improved testosterone recovery when compared to traditional injectable ADT agents. In a phase 3 clinical trial, a secondary analysis compared testosterone recovery in patients taking oral relugolix compared to leuprolide. In this trial, 54% of patients taking relugolix recovered to normal (280 ng/dL) testosterone levels at 3 months compared to 3% of patients taking leuprolide.[10] The results of our study are not directly comparable to those of Shore et al as our study was not able to stratify time to recovery given limitations from its retrospective design. However, it is interesting to consider that

degarelix, the injectable GNRH antagonist in this study, had no significant difference in overall rate of testosterone recovery when compared to other injectable lutenizing-releasing hormone agonists. Thus, it is interesting to consider if the route of medication administration plays an important role in the testosterone recovery rather than specific mechanism of action.

Limitations of this study include its retrospective design, small sample size, and homogenous ethnicity of the study population. Baseline lab values were not routinely collected prior to the onset of ADT, so many of the patients did not have a baseline testosterone value recorded. Baseline testosterone and SHBG levels have been shown to be an independent risk factor for testosterone recovery.[7,9] Additionally, testosterone levels during and after treatment were collected only at the discretion of the treating physician and are not collected at standard intervals. The lack of standard testosterone level collection also contributed to small sample size, as many eligible patients who had undergone ADT at our institution were excluded from the study due to lack of available testosterone values. Future studies should be planned as prospective studies in order to standardize baseline lab value collection and implement a testosterone value collection schedule. The relationship between specific LHRH agonists and testosterone recovery should also be studied. Additionally, nearly all patients included in the study were Caucasian, possibly reflective of the patient demographics of our rural Midwestern institution where this study took place. Future studies should seek to recruit a patient population more representative of all races, especially because prostate cancer occurs at a higher incidence in Black Americans.[1]

In conclusion, our findings confirm previous findings that age and duration of ADT carry greater risk for testosterone non-recovery. Additionally, our findings also demonstrated a novel association between an individual ADT agent (goserelin) on testosterone recovery. If correct, this has important implications regarding the selection of specific ADT agents. □

References

1. Brawley OW. Prostate cancer epidemiology in the United States. *World J Urol* 2012;30(2):195-200.
2. Singer EA, Golijanin DJ, Miyamoto H, Messing EM. Androgen deprivation therapy for prostate cancer. *Expert Opin Pharmacother* 2008;9(2):211-228.
3. Chen AC, Petrylak DP. Complications of androgen deprivation therapy in men with prostate cancer. *Curr Oncol Rep* 2004;6(3): 209-215.
4. Nguyen PL, Alibhai SMH, Basaria S et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* 2015;67(5):825-836.
5. Murthy V, Norman AR, Shahidi M et al. Recovery of serum testosterone after neoadjuvant androgen deprivation therapy and radical radiotherapy in localized prostate cancer. *BJU Int* 2006;97(3):476-479.
6. Yoon FH, Gardner SL, Danjoux C, Morton G, Cheung P, Choo R. Testosterone recovery after prolonged androgen suppression in patients with prostate cancer. *J Urol* 2008;180(4):1438-1444.
7. Nam W, Choi SY, Yoo SJ et al. Factors associated with testosterone recovery after androgen deprivation therapy in patients with prostate cancer. *Investig Clin Urol* 2018;59(1):18-24.
8. Tsumura H, Satoh T, Ishiyama H et al. Recovery of serum testosterone following neoadjuvant and adjuvant androgen deprivation therapy in men treated with prostate brachytherapy. *World J Radiol* 2015;7(12):494.
9. Spiegel DY, Hong JC, Oyekunle T et al. A nomogram for testosterone recovery after combined androgen deprivation and radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2019;103(4):834-842.
10. Shore ND, Saad F, Cookson MS et al. Oral relugolix for androgen-deprivation in advanced prostate cancer. *New Engl J Med* 2020;382(23):2187-2196.