Androgen deprivation therapy before radical prostatectomy is associated with poorer postoperative erectile function outcomes

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Study Type – Therapy (case series)
Level of Evidence 4

What's known on the subject? and What does the study add?
Erectile dysfunction is a recognized complication of radical prostatectomy. Androgen deprivation therapy adversely impacts sexual function.

Our study shows that the preoperative use of androgen deprivation therapy significantly reduces erectile function recovery after radical prostatectomy. The underneath pathophysiological mechanisms for this to occur are reviewed.

OBJECTIVE

- To define the impact of androgen deprivation therapy (ADT), undergone before radical prostatectomy (RP), on erectile function (EF) recovery.

MATERIAL AND METHODS

- A total of 38 consecutive patients presenting to a sexual medicine clinic after undergoing RP who had received ADT before RP (ADT+ group) were compared with a contemporary, age and comorbidity-matched cohort of 94 patients who did not receive ADT (ADT- group) before undergoing RP.
- Medical records were reviewed for demographics, comorbidity profiles and duration of ADT exposure.
- All the patients underwent Doppler penile ultrasonography within 6 months of RP and were administered the International Index of Erectile Function (IIEF) questionnaire.
- All the patients underwent evaluation of EF recovery. We analysed the incidence of venous leak (VL), mean IIEF EF domain score and proportion of men with EF domain scores ≥24 at 18 months after RP.

RESULTS

- The mean age, comorbidity profiles, median Gleason score, median pre-treatment PSA level, and mean time to evaluation after RP were similar between the two groups.
- The median duration of ADT exposure in the ADT+ group was 3 months.
- The incidence of VL within 6 months of surgery was 60% for the ADT+ and 20% for the ADT- group ($P < 0.001$). Likewise, the IIEF EF domain scores and proportion of men with EF domain scores ≥24 at 18 months were significantly lower in the ADT+ group, even when controlled for nerve-sparing status.

CONCLUSION

- Our data suggest that preoperative use of ADT adversely impacts EF outcomes and should therefore be avoided in the absence of robust data suggesting any oncological benefit.

KEYWORDS

androgen, prostate cancer, castration, hormonotherapy, erectile function, penile rehabilitation

INTRODUCTION

Erectile dysfunction (ED) is a recognized complication of radical prostatectomy (RP) and has a negative impact on health-related quality of life [1]. The cited rates of ED after RP vary widely, ranging between 20 and 90% [2]. The pathophysiology of ED after RP involves three factors; namely, neural injury, vascular injury and smooth muscle damage [3,4].

To date there are no robust data supporting an oncological benefit of undergoing androgen deprivation therapy (ADT) before RP. In a Cochrane review and meta-analysis, neoadjuvant ADT before RP was shown to substantially improve local pathological variables such as organ-confined rates, pathological down-staging, positive surgical margins and rate of lymph node involvement [5]. However, neither a significant increase in overall survival (odds ratio [OR] 1.11; 95%, CI: 0.67–1.85), nor an increase in disease-free survival was evident compared with RP without neoadjuvant ADT (OR 1.24; 95%, CI: 0.97–1.57) [5]. Despite these data, our experience has been that some patients are still being treated with ADT before undergoing RP.

In animal models, it is widely accepted that castrate testosterone levels result in erectile tissue structural alterations with the

TABLE 1 Patient demographics of the ADT+ and ADT- groups of patients

Patient demographics	ADT+, *n* = 38	ADT–, *n* = 94	*P*
Mean (SD) patient age, years	64 (13)	67 (9)	NS
Mean (SD) time after RP evaluation, months	5 (4)	6 (2)	NS
Comorbidity status, %			
1 vascular risk factor	58	50	NS
2 vascular risk factors	20	25	NS
≥3 vasculcar risk factors	22	25	NS
Clinical stage, %			
T1	50	54	NS
T2	35	32	NS
T3	15	14	NS
Mean (SD) pre-treatment PSA level	5.6 (3.6)	6.2 (4.2)	NS
Median Gleason sum	7	7	NS
Nerve-sparing RP status			
Bilateral	60	74	0.01
Unilateral	8	13	NS
Non-nerve-sparing	32	13	0.02
Preoperative sexual intercourse ability, %	86	88	NS

NS, nonsignificant.

development of subsequent venous leak (VL) [6–8]. The development of castrate testosterone levels in men is believed to result in corporal smooth muscle structural alterations after a threshold period of exposure to ADT [9–12]. The exact duration of ADT exposure required for this to occur is unknown, however, as short a time period of 4 months is known to worsen erectile function(EF) outcomes in patients treated with radiation therapy for prostate cancer [13].

It has been our experience that men treated with neoadjuvant ADT before RP have poorer EF outcomes after surgery. The present analysis was undertaken to define the impact of ADT before RP on EF recovery.

METHODS

STUDY POPULATION

Patients presenting to a sexual medicine clinic after RP, who had received ADT before undergoing RP (ADT+ group), were compared with an age and comorbidity-matched group of patients who did not receive ADT before undergoing RP (ADT- group). The duration of the ADT was defined on review of the patients' medical records. All patients (both groups) underwent duplex Doppler penile ultrasonography (DUS) within 6 months of RP. Age, comorbidity and prostate cancer information was obtained from a prospectively constructed database.

OUTCOME ASSESSMENT

The primary endpoint of the present analysis was the EF domain (EFD) of the international index of erectile function (IIEF) questionnaire. The questionnaire was administered to all patients after RP at least annually. Patients were instructed to answer the questions pertaining to EF, with or without the use of phosphodiesterase type 5 (PDE5) inhibitors. The follow-up schedule was identical for all patients with visits scheduled every 4 months after surgery. We analysed: (i) the mean IIEF EF domain score; (ii) the proportion of men with EF domain scores ≥24 at ≥18 months after RP; and (iii) the results of the DUS, specifically, the presence of (VL). Notably, no IIEF data were available preoperatively, as patients were seen for the first time by the sexual medicine clinician only after the RP. DUS was conducted using a vasoactive agent-redosing schedule, using trimix (papaverine, phentolamine and prostaglandin E1) to maximize corporal smooth muscle relaxation and reduce false diagnosis of VL. Standard parameters were used for the diagnosis of VL (End Diastolic Velocity (EDV) > 5 cm/s) and arterial insufficiency (Peak Systolic Velocity (PSV) < 30 cm/s).

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS for Windows (SPSS 16, SPSS, Chicago, IL, USA). We used the chi-squared test to evaluate associations between categorical variables. We used the Mann–Whitney *U*- and Kruskal–Wallis tests to compare the distribution of continuous/ordinal variables between groups defined by categorical variables. A forward stepwise model selection was used to identify independent predictors of EFD score ≤10 at ≥18 months after RP, using a logistic regression model. All independent variables that achieved univariable statistical significance at the 0.20 level were considered in step 1 of the stepwise logistic regression. The variables assessed included: patient age, degree of nerve-sparing (any nerve-sparing vs none), pathological stage (≥pT2 vs pT1), Gleason score (≥7 vs ≤6), exposure to neo-adjuvant ADT (yes vs no), and the number of vascular comorbidities (3 vs ≤2).

RESULTS

PATIENT POPULATION

A total of 38 patients formed the ADT+ group and 94 patients the ADT- group. The mean (SD) ages in the ADT+ and ADT- groups were 64 (13) years and 67 (9) years, respectively with no significant difference between the two groups. The mean (SD) time to evaluation after RP was similar for both groups (3.2 [1.4] months) with 78% of all DUS studies conducted before the 6th postoperative month. All except three patients had ADT using leuprolide acetate (LUPRON®, Abbott Laboratories, Abbott Park, IL, USA), the remaining patients receiving goserelin (ZOLADEX®, AstraZeneca, Wilmington, DE, USA). Of 38 patients, 26 (68%) received a single 3-month injection, the remainder (32%) received a single 4-month injection before RP. Patient demographics, comorbidity profiles and prostate cancer data are presented in Table 1, but were very similar between both groups. The most significant difference between groups was the nerve-sparing

status of the groups, with higher rates of bilateral nerve-sparing in the ADT- group and higher rates of non-nerve-sparing RP in the ADT+ group.

EF OUTCOMES

The incidence of VL within 6 months of surgery was 60% for patients in the ADT+ and 20% for patients in the ADT- group ($P < 0.001$; Fig. 1). When comparing VL incidence based on nerve-sparing status, the ADT+ group had a higher incidence of VL compared with the ADT- group for similar degrees of nerve-sparing. Likewise, the IIEF EF domain scores and proportion of men with EF domain scores ≥24 at 18 months were lower in the ADT+ group, even after controlling for nerve-sparing status (Figs 2 and 3). On multivariable analysis, factors predicting severe ED (EFD ≤10) > 18 months after RP included: patient age (OR = 1.8, $P < 0.05$), non-nerve-sparing surgery (OR = 8.4, $P < 0.001$) and neoadjuvant ADT exposure (OR = 12.8, $P < 0.001$ [Table 2]).

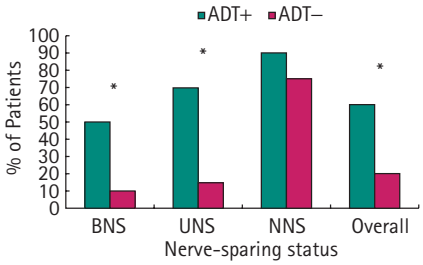
DISCUSSION

It has been shown that the pathophysiology of permanent and, in particular, medication-refractory ED is heavily predicated upon the presence of VL, generally thought to be induced by neuropraxia-associated erectile tissue damage, including collagenization of cavernosal smooth muscle [8,14,15].

Although the preservation of the neurovascular bundles during RP is essential for postoperative EF recovery, it is not sufficient to maintain cavernous nerve function because some degree of neural trauma occurs even in the absence of macroscopic nerve damage. As Mullerad *et al.* [16] have shown, in the rat cavernous nerve injury model, cavernous nerve exposure alone, without any direct injury, results in ED. Masterson *et al.* [17] showed that even the use of a Foley catheter during RP to apply tension on the lateral pedicles was associated with impaired EF recovery after RP.

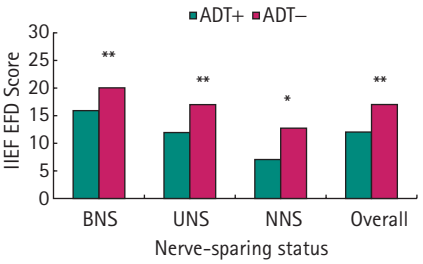
In the present analysis (Fig. 1), we have shown that the use of neoadjuvant ADT in the study population resulted in significantly higher rates of DUS-proven VL (60% vs 20%; $P < 0.01$). After controlling for nerve-sparing status, patients who underwent bilateral nerve-sparing and

FIG. 1. Compared incidence of venous leak within 6 months after radical prostatectomy in patients exposed to androgen deprivation therapy (ADT+) and patients without (ADT–) based on bilateral (BNS), unilateral (UNS), or non-nerve sparing (NNS) status.



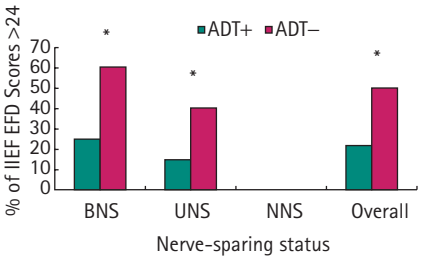
* $P < 0.01$

FIG. 2. Compared International Index of Erectile Function (IIEF) Erectile Function Domain (EFD) scores at 18 months after radical prostatectomy in patients exposed to androgen deprivation therapy (ADT+) and patients without (ADT–) based on bilateral (BNS), unilateral (UNS), or non-nerve sparing (NNS) status.



* $P < 0.01$;** $P < 0.05$

FIG. 3. Compared proportions of patients exposed to androgen deprivation therapy (ADT+) and patients without (ADT–) with an International Index of Erectile Function (IIEF) Erectile Function Domain (EFD) scores ≥24 at 18 months after radical prostatectomy based on bilateral (BNS), unilateral (UNS), or non-nerve sparing (NNS) status.



* $P < 0.01$

patients who underwent unilateral nerve-sparing surgery were 5 ($P < 0.01$) and 4.5 ($P < 0.01$) times more likely to have VL within the first 6 months after RP, respectively, if exposed to ADT before undergoing RP. Thus, ADT before RP minimized the benefit of nerve-sparing surgery. With regard to the IIEF EFD score, for all nerve-sparing grades, patients in the ADT+ group had significantly lower scores (Fig. 2). With regard to returning to an EFD score ≥24 with PDE5 inhibitor use ≥18 months after RP, patients in the ADT+ group were less likely to achieve this; only ≈ 25% of patients in the ADT+ group, who had undergone bilateral nerve-sparing RP, were able to achieve an EFD of ≥24 with PDE5 inhibitor treatment (Fig. 3). This proportion was even lower for patients who had undergone unilateral nerve-sparing surgery (15%). On multivariable analysis, patients in the ADT+ group were almost 13 times more likely to experience severe ED, as defined by an EFD score of ≤10 (Table 2).

Mechanistically, it is likely that ADT resulted in significant worsening of EF outcomes in a multifactorial fashion, including: (i) direct erectile tissue (smooth muscle and endothelium) damage in the absence of any testosterone; (ii) impairment of nerve regeneration; (iii) absence of erections; and (iv) a reduction in libido.

Firstly, androgens play a physiological role in maintaining the integrity of both smooth muscle and endothelium [9]. Androgens promote smooth muscle cell growth, are involved in the differentiation of progenitor vascular stroma cells and in the response to

TABLE 2 Multivariable analysis of predictors of severe ED (IIEF EFD ≤ 10)

	OR	95% CI	*P*
Patient age	1.8	1.2–2.3	<0.05
Non-nerve sparing	8.4	2.2–13.6	<0.01
ADT exposure	12.8	4.6–23.7	<0.001

endogenous vasodilators, and regulate connective tissue metabolism [18]. Absence of androgens is therefore likely to impair EF through the alteration of the same structures affected by cavernous neurapraxia, thus amplifying the neural injury and impairing EF recovery. This has been clearly shown in animal models. In a study performed on rats, androgen

deprivation by surgical or medical castration resulted in reduction in smooth muscle content and structural alterations in the corpus cavernosum leading to VL [7]. Castrated dogs have been shown to have significantly higher cavernosal collagen/smooth muscle ratios [19]. The impact of the presence of VL in men is that their ability to recover natural or PDE5 inhibitor-assisted erection is poor. Mulhall *et al.* [20] showed that only 8% of men who had VL after RP had recovery of spontaneously functional erections.

Secondly, as androgens have a neuroprotective role, it is also plausible that a complete absence of testosterone impairs cavernous neuroregeneration, thus amplifying the effect of cavernous neuropraxia. In one study [21], two weeks after rat castration, a significant increase in ultrastructural alterations was seen in the dorsal nerve of the rat penis compared with control rats. In a study performed in male rats, intracavernosal pressure elicited with electrical stimulation of the cavernous nerve was significantly lower in castrated male rats compared with the intact controls and furthermore, testosterone replacement was capable of restoring EF [22].

Thirdly, current animal and some human data support the use of PDE5 inhibitors and the generation of early erections after RP as a strategy to improve EF recovery [23]. Indeed, a factor that protects cavernosal smooth muscle from collagenization and subsequent VL development may be the oxygenation of erectile tissue. One of the main physiological factors contributing to the maintenance of good cavernosal oxygenation is erection itself, in the early stages after RP, often dependent on the use of PDE5 inhibitors [20]. In a small study on sexually active patients, administration of an LHRH agonist induced significant changes in frequency, magnitude, duration and rigidity of nocturnal erections in all patients [24]. If one considers the fact that men have a mean number of 3–6 erections per night, it is easy to understand the importance of this consequence. Furthermore, it is becoming increasingly appreciated that low testosterone levels result in impaired PDE5 inhibitor response [25].

Finally, the often absent libido generally associated with ADT-induced agonadism may interfere with patients' motivation to use PDE5 inhibitors in the early stages after RP [26]. In addition to this, cessation of ADT does not result in instantaneous reversal of the agonadal state. Several studies have shown that castrate testosterone levels last long after the end of the ADT treatment [27]. After a single injection of a 3-month buserelin implant 9.45 mg, the mean (range) time to first return of testosterone above the castrate range was 246 (168–344) days [28]. Similar results were found by Kaku *et al.* [29] where median time to normalization of testosterone levels after a single 3-month LHRH agonist injection was 23 months [29], with increased time for such recovery in elderly patients (>65 years old) and in patients who received ADT for 30 months or longer [29]. In another study on 20 men treated with neoadjuvant long-term ADT, the median time to recovery of normal luteinizing hormone levels was 4 months, compared with 8 months to reach supra-castrate total testosterone levels, and 2.3 years to reach normal total testosterone levels [30].

The clinical implication of the present data is clearly that, in the absence of compelling data supporting the use of ADT before RP to improve oncological outcomes, ADT should be avoided before RP as it translates into significantly reduced EF. The limitations of the present study include the small patient numbers, which is largely related to the infrequent application of neoadjuvant ADT in the population who underwent RP. The absence of preoperative IIEF data is a weakness, although all patients had self-reported fully functional erections without the use of any erectile aids before ADT exposure. Another limitation is the absence of a grading system for cavernous nerve-sparing and the number of surgeons in this analysis (five) rendering comparison of nerve-sparing from surgeon to surgeon somewhat difficult. Finally, testosterone levels were measured in very few patients after surgery (in either group), therefore, it is unclear for how long patients in the ADT+ group were at castrate levels and furthermore, it is unclear if any patients in the ADT- group were hypogonadal. A major strength, however, is that all patients had postoperative EF assessment using a validated tool, the IIEF, and had VL proven by duplex DUS.

In conclusion, the present data suggest that the use of neoadjuvant ADT before RP adversely affects EF outcomes after RP and, in the absence of compelling data supporting its use, it should be avoided in the RP population.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **ADT**, androgen deprivation therapy; **RP**, radical prostatectomy; **EF**, erectile function; **IIEF**, International Index of Erectile Function; **DUS**, Doppler penile ultrasonography; **VL**, venous leak; **EDV**, End Diastolic Velocity; **PSV**, Peak Systolic Velocity; **ED**, Erectile dysfunction; **OR**, odds ratio; **EFD**, erectile function domain; **PDE5**, phosphodiesterase type 5.