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Brief Report

Potential primary prevention of Peyronie's disease post prostatectomy?—retrospective analysis of peri-operative multi-modal penile rehabilitation

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Abstract: The surgical management of prostate cancer through radical prostatectomy has the potential to impact patients' sexual function, including erectile dysfunction and Peyronie's disease (PD). Historical data suggests the incidence of PD in post-prostatectomy patients is higher than in the general population at 15.9%. Our study objective was to measure the rate of the development of PD among patients that receive penile rehabilitation (PR) regimen prior to and immediately after radical prostatectomy. In this study, we retrospectively reviewed the charts of 581 patients who were diagnosed with prostate cancer, treated with radical prostatectomy, and engaged in a PR program. Patients with the diagnosis of PD prior to prostatectomy were excluded from this study. The PR program consists of daily tadalafil, L-citrulline, and weekly vacuum erectile device with the option of intracavernosal injections if patients fail to respond to the regular regimen. We found the incidence of PD to be 2.9%, suggesting that PR regimens programs may be associated with a reduced incidence of PD in post-prostatectomy patients. Ten (out of 17) patients were diagnosed with PD after 2 years of follow up. The return of erections was not statistically different among patients who developed PD and the rest of the patients. Prospective, multi-institutional trials will be required to elucidate whether PR can prevent the development of PD in this patient population.

Keywords: Peyronie's disease (PD); radical prostatectomy; penile rehabilitation (PR); erectile dysfunction (ED)

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Introduction

Prostate cancer is the most prevalent cancer in men, accounting for 3.8% of all cancer-related deaths worldwide (1). Radical prostatectomy remains the cornerstone treatment option for localized prostate cancer (2). Despite advances in surgical techniques, the prevalence of post-operative erectile dysfunction (ED) remains as high as 46% for robotic-assisted radical prostatectomy (RALP) and up to 82% after retropubic radical prostatectomy (RRP) (3). Furthermore, a study in 2010 also reported the incidence of Peyronie's disease (PD) after RALP to be 15.9%, significantly greater than the 0.5–7.1% prevalence in the general population (4,5).

PD refers to acquired penile curvature and is defined as a condition in which fibrous scar tissue forms within the tunica albuginea of the penis. The exact cause of PD following RALP is not well understood, though endothelial dysfunction, diminished blood flow, diseases of collagen, and development of fibrosis from repeated micro-injuries to the penile tissue have been postulated as potential hypotheses (4-8). Smoking, diabetes, and hypertension have also been shown to be linked with PD (4,8,9). The exact reason for

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this is unknown, but the unifying hypothesis is that these etiologies all lead to inflammation and microvascular disorders that limit the supply of blood (10).

Radical prostatectomy has also been linked to PD for possibly the same reasons. During RALP, the surgeon may manipulate the tissues and nerves surrounding the prostate gland that is important for the integrity and function of the penis. This could lead to microtrauma, lack of blood supply, disruption of the innervation to the penis, and pro-fibrotic changes which could in turn lead to PD (4,11). Once diagnosed, PD is very difficult to treat and its psychological and physical effects on patients' quality of life is severe (12). Studies have identified psychological distress, depression, anxiety, sexual dissatisfaction, and disruptions in relationships associated with PD (12,13).

To improve erectile function recovery after RALP, penile rehabilitation (PR) is often recommended throughout post-surgery follow-up care. PR often involves the use of approaches that improve blood flow to penile tissue. These approaches often include some variation of daily phosphodiesterase type 5 (PDE5) inhibitors, vacuum erectile devices (VEDs), L-citrulline supplementation, and intracavernosal injections (ICI). The components of PR have previously been shown to improve penile blood flow and aid in the return of erections adequate for sexual activity post-op, including in a recent prospective, randomized controlled study (14-16).

To our knowledge, this is the first study that have evaluates and reports on the incidence of PD in post-prostatectomy patients who used PR. In this retrospective review, our primary objective was to evaluate the rate of PD among our prostate cancer patients who have undergone a formal, multi-modal PR program that utilizes oral pharmacological agents (PDE5 inhibitors and L-citrulline, and ICI if indicated), mechanical intervention with VED, and lifestyle counseling. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-281/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the University of California, Los Angeles (UCLA) Institutional Review Board (IRB#22-001762) and individual consent for this retrospective analysis was waived. The study aims to retrospectively review the medical records of all patients who have undergone RALP from January 2016 to January 2019. At our institution, all prostate cancer patients that are scheduled for RALP are referred to the Men's Health Clinic at UCLA, a comprehensive male sexual health clinic, to start their PR program and follow up regularly for their sexual health independent of the surgeon who performed their prostatectomy. The PR program is standardized for all patients, and it includes 5 mg tadalafil daily, 1,500 mg L-citrulline twice daily, and VED use at least twice a week. The recommended VED protocol is for the patient to apply the VED, engorge the penis with blood without the use of a constriction band, remove the device and wait for detumescence, and then repeat for a total of 10 repetitions. Men refractory to these therapies have the option to undergo further treatment with ICI (trimix: papaverine, alprostadil, phentolamine; or if experiencing a painful reaction to alprostadil, bimix: papaverine, phentolamine) as early as 3 months post-op. During each visit, patients were also counseled on the importance of sleep, maintaining a healthy diet, and exercise (14). We excluded patients who had PD pre-operatively or who did not see the providers in the Men's Health Clinic at UCLA for PR counseling.

The primary outcome of interest was the rate of PD among those who have undergone RALP and engaged in post-prostatectomy PR. Descriptive statistics were used to analyze our findings. A one-sample *t*-test was used to compare the return of erection among patients that went on to develop PD compared to the rest of the patients.

Results

After the exclusion of three patients that had PD pre-op, 581 patients with prostate cancer that received radical prostatectomy and engaged in PR were included in this analysis. Among this cohort, the incidence of PD was 2.9% (17/581). The demographics and sexual function of patients is depicted in *Table 1*. The average age of patients that developed PD was 62.6 [58–68] years old. There was no statistically significant difference in the return of erections among patients with PD compared to the rest of the patients (P>0.05). Among the 17 patients that developed PD, 2 were diagnosed within 12 months, 5 were diagnosed in the second-year post-op, and the remaining 10 patients were diagnosed after 24 months post-op. We have added this information in our results.

Discussion

ED, a well-studied potential side effect of radical

Table 1 Patient demographics and sexual function

Cohort characteristics	Follow up after radical prostatectomy for prostate cancer (n=581)
Age (years)	62.6 [58–68]
Race	
White	388 (66.8)
Black	53 (9.1)
Asian	33 (5.7)
Other	79 (13.6)
Unknown	28 (4.8)
Ethnicity	
Hispanic	51 (8.8)
Non-Hispanic	494 (85.0)
Unknown	36 (6.2)
Follow up for all patients (days)	643 [84–1,014.5]
Follow up for patients that developed PD (days)	1,168 [695–1,674]
Patients diagnosed with PD	17 (2.9)
Months after surgery until the diagnosis of PD	28.7 [20–36]

Values are presented as n (%) or median [IQR]. IQR, interquartile range; PD, Peyronie's disease.

prostatectomy, also arises, or progresses in cases of pre-operative ED, through the same mechanisms (11). Today, PR is considered the standard of care following radical prostatectomy to increase blood flow to the penis post-op to optimize recovery of erectile function, although different approaches and regimens are used by different providers. The use of PR has been shown to improve the return of erectile function and recently other researchers have corroborated these findings with a randomized controlled study demonstrating that a combination of oral PDE5i and VED therapy improves IIEF-5 scores and significantly higher rates of erectile function sufficient for penetration (14-16).

The peer-reviewed literature on the link between radical prostatectomy and PD is quite sparse. Some hypotheses have been suggested, such as trauma during surgery, disruption of the nerves supplying the penile tissue, however more extensive studies are needed to study this association (4,11). In this study, we hypothesized that in post-prostatectomy patients undergoing PR, the incidence of PD may be lower than historical cohorts. In a widely cited study, Tal *et al.* highlighted that 7.6% of patients after prostatectomy were found to have PD at 1 year, 13.7% at 2 years, and 15.9% at 3 years of follow-up in a cohort of 1,011 men (4). In our cohort of men who engaged in PR after prostatectomy, only 2.9% of patients (17) developed PD with a median follow-up of 1.8 years. The incidence of PD in a healthy population is estimated to be somewhere around 0.5% to 7.1% (5). While previous studies have demonstrated improved recovery of erectile function with the use of PR protocols, this is the first study to highlight the prevalence of PD in a population of patients using a post-prostatectomy PR protocol. This hypothesis-generating study should pave the way for future studies to evaluate whether PR regimens reduce the incidence of PD to levels similar to the general population.

There are several limitations inherent in the study type. First, there are no direct control or comparison groups as every patient that undergoes radical prostatectomy will be referred to Men's Health Clinic to initiate PR. Therefore, we cannot make any causation claims between PR and the incidence of PD. Furthermore, we relied on electronic health records (EHR) to identify cases of PD and track data. It is possible that there are cases not captured in the EHR and that patients may have developed PD but did not discuss their findings with our sexual health providers. Our institution is located in a major metropolitan area with additional hospitals and academic centers; therefore, we do not have access to follow-up data for patients that chose to go to another location for their follow-up care. Another limitation is that adequate rigidity post-op at clinic was not required to diagnose patients with a new PD. PD was diagnosed primarily as reported by patients using patient-taken photographs. As accurate curvature assessment would require proper rigidity during examination, we did not report the degree of curvature in this analysis.

These limitations notwithstanding, the possibility that PR could impact the development of PD in post-prostatectomy patients warrants further evaluation. For example, a future study could look at the stiffness and elasticity of tunica albuginea in patients that receive PR. A recent study has used penile shear wave elastosonography to assess elasticity of the tunica with promising results (17). Assessment of elasticity could further direct us in studying the biomechanical pathways that may impact PD in patients receiving PR. Like ED, PD impacts the physical, sexual, and psychological well-being of patients (18). These findings should pave the way for future studies that could

increase compliance with PR if data supports that sexual health and cancer survivorship is positively impacted by these regimens.

Conclusions

This is the first study that reports the rates of PD among prostate cancer patients that receive a standardized multimodal PR program peri-operatively. We found the incidence of PD in this population to be 2.9% which is similar to the rates reported for the general population, and lower than the rates reported for patients that do not receive PR following their radical prostatectomy. This analysis includes major limitations, including a lack of control group, however, given the significant impact of PD on patients sexual and psychological life, future well-designed studies are needed to further investigate the potential benefits of PR in preventing PD.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-281/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-281/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the University of California, Los Angeles (UCLA) Institutional Review Board (IRB#22-001762) and individual consent for this retrospective analysis was waived.

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