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Sexual Potency Preservation and Quality of Life Following Prostate Brachytherapy and Low-Dose Tadalafil

Thomas J. Pugh, M.D.¹, Usama Mahmood, M.D.¹, David A. Swanson, M.D.², Mark F. Munsell⁴, Run Wang, M.D.², Rajat J. Kudchadker, PhD.³, Teresa L. Bruno, C.M.D.¹, and Steven J. Frank, M.D.¹

¹Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

²Department of Urology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

³Department of Radiation Physics, The University of Texas M. D. Anderson Cancer Center, Houston, TX

⁴Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, TX

Abstract

Purpose—To prospectively determine sexual function, bother, and potency preservation in men treated with prostate brachytherapy and twice weekly tadalafil.

Methods—From 2005–2011, men treated with low dose rate prostate brachytherapy were treated on a prospective registration study. All patients were prescribed tadalafil 10 mg twice weekly. The expanded prostate cancer index composite (EPIC) questionnaire was administered prior to treatment and at each follow-up. A subgroup analysis of men with sexual potency at baseline was performed

Results—Two hundred thirty-seven men were analyzed. Median age was 64 years (range 44–86). Median follow-up was 24.8 months (range 1–60). At baseline, 175 (74%) reported erections firm enough for sexual activity and 148 (62%) were potent (erections firm enough for intercourse). Statistically significant changes in sexual function/bother were appreciated from baseline throughout the analysis period, though absolute changes were relatively small and did not meet criteria for clinical significance. At 24-month follow-up 72% reported erections firm enough for sexual activity and 56% were potent. Of men with potency at baseline, 89% had erections firm enough for sexual activity and 76% remained potent 24 months post-treatment.

Conclusions—Peri-procedural tadalafil and prostate brachytherapy resulted in high rates of sexual potency preservation and no clinically significant effect on sexual quality of life.

Corresponding author: Thomas J. Pugh, M.D., The University of Texas M. D. Anderson Cancer Center, 1840 Old Spanish Trail, Unit 1150, Houston, TX 77030; Tel: (713) 563-8961; Fax: (713) 563-8616; tpugh@mdanderson.org.

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Conflicts of interest: none

Introduction

Low dose rate (LDR) permanent prostate brachytherapy is a safe and highly effective treatment for men with organ confined prostate cancer.(1–3) Treatment involves the placement of small radioactive sources into the prostate gland in order to deliver radiation directly to the prostate. Because radiation dose delivery is inversely and exponentially related to the distance from the radiation source, radiation dose to the surrounding bladder, rectum, and connective tissue is minimized. LDR-prostate brachytherapy is more convenient than alternative treatments for prostate cancer as it can be delivered in a single outpatient visit. Erectile dysfunction (ED) is a common side effect of prostate cancer treatment, inclusive of prostate brachytherapy,(4) with affected patients suffering significant health related quality of life (HRQOL) consequences.(5–7) In men who are fully potent prior to prostate cancer treatment, sexual quality of life impairment is perhaps the strongest predictor of overall patient satisfaction.(5) Due in part to the complexity of sexual function, varying definitions of ED, and the historical absence of a standardized sexual quality of life instrument, high quality data on sexual function after prostate brachytherapy is limited.(8)

The term penile rehabilitation describes the use of medications or devices after definitive prostate cancer treatment delivered with the intent of preserving erectile tissue integrity and maximizing recovery of erectile function. The fundamental principle is to minimize post-treatment fibrosis of penile tissue through optimizing oxygenation and protecting endothelial cells.

Use of 5-phosphodiesterase inhibitors (PDE5i) with the intention of sexual quality of life preservation after prostate cancer treatment has been successfully implemented in men treated by radical prostatectomy.(9–11) While the primary mechanism of ED following prostatectomy is thought to be predominantly neurogenic(12), ED following radiation therapy is thought to be primarily vasogenic.(13) Following radiation therapy, sensitive endothelial cells lining penile arteries and the sinusoids of the corpora cavernosa can be damaged, leading to luminal stenosis, arterial insufficiency, and induction of fibrosis in the corporal tissue months to years after radiation treatment.(14,15) Hypoxia in the erectile tissue microvasculature appears to mediate the process of post-radiation fibrosis.(16,17) Achieving erections on a regular basis may prevent up-regulation of TGF- β , a cytokine believed to play a central role in post-radiation fibrosis.(18) PDE5i use facilitates periodic oxygenation of erectile tissues, promotes endothelial cell/smooth muscle vitality, and allows many patients to achieve increased erection rigidity.(19–23) Delayed initiation of PDE5i therapy in men with ED after prostate brachytherapy results in worse erectile function compared to early medical intervention.(24) All of the above suggest a role for peri-procedural PDE5i therapy in men treated with prostate brachytherapy. The current study reports the results of a prospective cohort of men treated with prostate brachytherapy and peri-procedural tadalafil for penile rehabilitation.

Materials and Methods

Patient Selection and Treatment

The overseeing institutional review board approved patient data collection and analysis. All participants provided written informed consent for treatment. Patients treated with prostate brachytherapy monotherapy were eligible for analysis. Criteria for prostate brachytherapy monotherapy during the analysis period were generally restricted to the following: AJCC 7th edition clinical stage T1c-T2c, presenting PSA <15 ng/ml, and Gleason score ≤ 7. Men with contra-indications to PDE5i were excluded from participation. Men endorsing any of the following were also excluded from analysis: any prior PDE5i use, use of other sexual medications including intra-cavernosal injections, use of sexual devices for erection enhancement, receipt of androgen deprivation therapy with therapeutic or cytoreductive intent, or receipt of supplemental external beam radiation therapy. Men with penile prostheses were also specifically excluded.

All patients were prescribed tadalafil 10 mg po twice weekly starting 2 weeks prior to prostate brachytherapy. The dosing and schedule of tadalafil was based on the intention of encouraging spontaneous erections twice weekly. No specific duration of therapy was pre-determined, however, continuation of tadalafil was encouraged for at least 6 months after the prescribed radiation dose was delivered (approximately 6 isotope half-lives). All patients were treated with iodine-125, palladium-103, or cesium-131 brachytherapy seeds to prescribed doses of 145 Gray (Gy), 125 Gy, and 115 Gy respectively. A standard ultra-sound guided, trans-perineal technique utilizing pre-loaded brachytherapy needles was used for all procedures. No patient received supplemental external beam radiation or androgen deprivation therapy.

Assessment of sexual function and bother

The expanded prostate cancer index composite (EPIC) and companion utilization of sexual medications and devices questionnaire are validated prostate cancer specific instruments for assessment of patient reported outcomes.⁽²⁵⁾ All patients completed the EPIC questionnaires prior to initiation of study treatment (baseline) and at regular follow-up intervals (1, 4, 8, 12 months post-brachytherapy and every 6 months thereafter). Sexual function, bother, and summary scores were tabulated according to instrument guidelines scaled from 0–100; where lower scores represent worse sexual function and more bother. The companion utilization of sexual medications and devices questionnaire was co-administered at each assessment time-point and is inclusive of patients reported sexual potency in the absence of pharmaceutical or mechanical enhancement.

Definition of potency

Data regarding potency was derived from patient responses to EPIC-26 question #18 “How would you describe the quality of your erections during the last four weeks” with possible responses limited to the following: 1) None at all 2) Not firm enough for any sexual activity 3) Firm enough for masturbation and foreplay only 4) Firm enough for intercourse. Potency was defined as erections firm enough for sexual intercourse. Men reporting erections firm enough for sexual intercourse, masturbation, or foreplay were defined as having erections

firm enough sexual activity. Preservation of sexual potency and sexual activity was determined through subgroup analysis at baseline and subsequent follow-up.

Statistical Analysis

A paired t-test was used for statistical comparisons to baseline with statistical significance defined as $p < 0.05$. The scores were plotted against assessment time as a graphical aid to visualize changes over time. Clinical significance as used in this study represents a meaningful change in the patient's reported quality of life defined objectively as a change that is greater than half the standard deviation (SD) of the baseline score. This definition of clinical significance is consistent with statistical principles for psychometric testing. (26)

Results

Patient Characteristics

Two hundred thirty-seven men were eligible for analysis. The median age was 64 years (range 44–86). The median follow-up was 24.8 months (range, 1–60). One hundred seventy-five men (74%) reported erection firm enough for sexual activity at baseline. Of these men, 148 (62% of total) were potent with “erections firm enough for intercourse”, 27 (11% of total) reported erections “firm enough for masturbation and foreplay only”, 23 (10% of total) reported erections “not firm enough for any sexual activity”, and 39 (17% of total) reported “no erections” at baseline. Demographic and clinical characteristics of the study sample are summarized in Table 1.

Preservation of sexual potency

For all respondents, 70% and 72% reported erections firm enough for sexual activity at 12 and 24 months post-treatment demonstrating a net change from baseline of -4% and -2% respectively. Potency was reported by 48% and 56% of respondents at 12 and 24 months representing a net change of -14% and -6% respectively. The change in potency over time for all patients is represented in Figure 1.

Men with potency at baseline were likely to preserve erections firm enough for sexual activity. Of the 148 men reporting erections firm enough for sexual activity at baseline, 90% and 89% reported preservation of this function at 12 and 24-months post-treatment, respectively. However, potency was observed to decline following therapy, as 31% and 24% experienced a loss of potency at 12 and 24 months following treatment. (Figure 2).

Sexual function and bother

The mean $\pm$ standard deviation sexual summary, function, and bother scores at baseline were 57.5 ± 26.7 , 50.9 ± 27.9 , and 72.8 ± 31.8 respectively. There were statistically significant changes in sexual summary scores at each follow-up assessment (all patients). At 12 months the sexual summary change was -8.5 ($p < 0.0001$), and at 24 months the sexual summary change was -9.4 ($p < 0.0001$). None of the post-treatment changes were clinically significant. For the subset of potent patients at baseline, the change at 12 months was -6.3 ($p = 0.006$) and the change at 24 months was -5.5 ($p = 0.013$).

Statistically significant changes in sexual function were appreciated at each follow-up time point. The mean change in sexual function score at 12 and 24 month follow-up was -7.5 ($p < 0.001$) and -8.7 ($p < 0.001$). Neither of these changes was clinically significant. Statistically significant changes in sexual bother were also appreciated at each post-treatment assessment. The mean change in sexual bother score at 12 and 24 month follow-up was -10.5 ($p < 0.001$) and -11.1 ($p < 0.0001$). No clinically significant changes were appreciated at any time-point. Figure 3 illustrates the change in sexual summary, function, and bother scores over time.

Significantly more patients reported worse erection frequency, sexual function, distress from poor erections, and overall sexual distress at both 12-months and 24-months following prostate brachytherapy compared with baseline. More patients reported poor erection quality compared to baseline at the 12-month and 24-month follow-up; however this difference was statistically significant at 12-months only ($p = 0.01$ at 12-months; $p = 0.26$ at 24-months). There were no statistically significant differences in the percent of patients who expressed distress from an inability to reach orgasm at 12 or 24 months compared to baseline. Fifty-two percent and 47 percent of respondents reported continued use of tadalafil at 12 and 24 month follow up respectively. Table 2 summarizes the levels of sexual distress and dysfunction over time.

Discussion

To our knowledge, this study is the first ever prospective assessment of peri-procedural PDE5i use with radiation therapy using a validated instrument for measurement of sexual function and bother. In this study evaluating the application of low dose tadalafil as penile rehabilitation following prostate brachytherapy, no clinically significant differences in patient reported sexual function or bother were appreciated. The sexual function preservation was relatively high with approximately 90% of men with erections firm enough for any sexual activity at baseline maintaining this ability and 76% of men with potency at baseline experiencing no detrimental effect on their sexual potency 2-years after prostate brachytherapy. Despite statistically significant differences in sexual function at all time-periods post-treatment compared to baseline, the absolute change from baseline was relatively small and did not result in worse sexual bother two years post-treatment.

Sexual function and potency preservation using the study regimen is modestly superior to other contemporary brachytherapy series using the EPIC to record patient quality of life. The Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROSTQA) trial is a prospective, longitudinal, multi-center cohort of men with previously untreated localized prostate cancer who elected prostatectomy, external beam radiation therapy, or brachytherapy as primary treatment. Data were collected via telephone interview using the EPIC survey and companion utilization of sexual medications and devices. Sanda et al. reported the initial urinary, bowel, sexual and hormonal quality of life changes over time following prostate cancer treatment.⁽⁵⁾ Alemozaffer et al. recently published an additive secondary analysis through development of a multivariate model to predict ED after prostate cancer treatment using the EPIC data from PROSTQA with external validation using patients from the Cancer of the Prostate Strategic Urologic Research Endeavor

(CaPSURE) database.(27,28) In the patients from PROSTQA treated with prostate brachytherapy (n = 247), 43% reported the ability to attain functional erections suitable for intercourse at 2-years; this compares to 56% in the current study using low-dose tadalafil.

Our study is unique from prior series in that patients who used sexual medications or devices at baseline were excluded. The use of PDE5is is common in the demographic of men diagnosed with prostate cancer.(28,29) For example, 31% of patients treated with prostate brachytherapy in PROSTQA reported use of sexual medications or devices at baseline. Initiation of PDE5is after radiation treatment for prostate cancer is also common and highly effective.(30–35) In PROSTQA, 47% of men treated with prostate brachytherapy used sexual medications or devices 24-months following treatment with a higher incidence (54%) of use in men who reported optimal potency at baseline. PDE5is were the most common intervention for erectile dysfunction; with intra-urethral alprostadil, penile injections, vacuum erection devices, and penile prostheses used less frequently. As a result, one might make the argument that comparing the current study to PROSTQA represents a comparison of early versus delayed intervention. Interestingly, while the incidence of sexual medication and device use over time increased in PROSTQA, almost half of the men treated on the current study discontinued supportive measures over time. This finding suggests early intervention with PDE5is may reduce the need for erectile dysfunction support long-term.

Our study has several limitations including the following: 1) The optimal methodology for assessing a treatment regimen such as this is a randomized, placebo controlled trial. Although we entertain a comparison of our results to the PROSTQA study as a historical control, the treatment period of the current cohort occurred predominantly prior to reporting of PROSTQA. Therefore, our analysis was neither designed nor powered for direct comparison to PROSTQA. Furthermore, the absence of a control group invalidates our ability to adjust for an increasing prevalence of ED with age. Considering the complexity of sexual function and satisfaction, our results are likely influenced by extrinsic and/or intrinsic variables best controlled through randomization. Our results should be interpreted cautiously as they are likely influenced by differences between patient groups and selection bias. Thus, these results should be considered hypotheses generating as opposed to conclusive. 2) Although sexual function and bother appear to stabilize after 24-months post treatment, the median follow-up of the current study is relatively short when considering fibrotic effect post-radiation, which can occur several years following therapy. Longer follow-up of this cohort is desirable. 3) The dosing and schedule of tadalafil for this study was determined based upon the concept of promoting spontaneous erections at least twice per week. A conservative dose of 10 mg twice weekly was chosen to minimize cross-reactivity with other commonly prescribed medications following prostate brachytherapy (ie. selective alpha-blockers). While conventional dosing of daily tadalafil (5 mg) has been shown to prevent corporal fibrosis and veno-occlusive dysfunction following cavernous nerve resection, it is unclear whether the same physiologic response occurs with the dose/schedule used in our cohort. The Radiation Therapy Oncology Group (RTOG) recently completed accrual of a phase III randomized, placebo controlled trial comparing daily tadalafil (5 mg) versus placebo in men treated with radiation therapy for prostate cancer. The results of this trial are pending and should clarify the role of PDE5is as penile rehabilitation after radiation therapy.

In conclusion, men with prostate cancer treated with prostate brachytherapy and low-dose tadalafil twice weekly were highly likely to maintain their sexual potency. Early treatment with PDE5is may reduce the need for subsequent therapeutic use of sexual medications and devices after prostate brachytherapy. The optimal method for penile rehabilitation after radiation treatment has yet to be defined and requires further investigation.

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LIST OF ABBREVIATIONS

LDR	low dose rate
ED	erectile dysfunction
HRQOL	health related quality of life
PSA	prostate specific antigen
PDE5i	5-phosphodiesterase inhibitors
Gy	Gray
EPIC	expanded prostate index composite
RTOG	Radiation Therapy Oncology Group

Figure 1. Sexual potency for all respondents treated with prostate brachytherapy and twice weekly tadalafil. (A) Erection quality over time (B) Percentage of all patients reporting erections firm enough for sexual activity over time.

Figure 2.
Potency preservation following prostate brachytherapy and twice weekly tadalafil.

Figure 3. Expanded prostate cancer index composite sexual domain scores following prostate brachytherapy and twice weekly tadalafil.

Table 1

Baseline demographics and clinical features for the study population

Characteristic	Value
Median Follow-Up (Range)	24.8 (1–60) months
Median Age (Range)	64 (441–86) years
Race (%)	
White	187 (81)
Black	28 (12)
Hispanic	12 (5)
Other	4 (2)
Clinical Stage (%)	
T1c	197 (86)
T2a	28 (12)
T2b	4 (2)
T3b	1 (0.4)
Gleason Score (%)	
6	94 (41)
7	136 (59)
9	1 (0.4)
Mean PSA (Range)	5.51 (0.101–67.00) ng/mL
Mean Baseline EPIC Sexual Score Total (Standard Deviation)	
Function	50.9 (27.9)
Bother	72.8 (31.8)
Summary	57.5 (26.7)
Hypertension (%)	
Yes	135(59)
No	95 (41)
Tobacco Smoking (%)	
Yes	56 (25)
No	171 (75)
Diabetes Mellitus (%)	
Yes	21 (9)
No	210 (91)

Table 2

Percentage of patients reporting sexual dysfunction or distress after prostate brachytherapy and twice weekly tadalafil

Months After Brachytherapy	0	4	8	12	18	24
Poor erection quality	38	51	50	52*	52	44
Poor erection frequency	34	49	51	55*	58	54*
Poor sexual function	30	42	44	46*	47	42*
Distress from poor erections [†]	22	34	32	35*	37	35*
Distress from inability to reach orgasm [†]	22	30	31	25	27	31
Overall sexual distress [†]	18	28	27	28*	26	25*

[†] Responses were dichotomized on the basis of the response that the quality-of-life concern was “a moderate or big problem.”

* p <0.05 compared to baseline. Comparisons performed at 12 and 24 months only.