Association between erectile function and lower urinary tract symptoms in patients treated with permanent seed prostate brachytherapy

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Purpose: *Among men who underwent permanent seed prostate brachytherapy, we aimed to: 1) investigate: whether development of lower urinary tract symptoms (LUTS) after permanent seed prostate brachytherapy was associated with suboptimal erectile function before brachytherapy, and 2) identify factors that are associated with normal erectile function before brachytherapy.*

Methods and materials: *We analyzed data from 215 consecutive patients with low- or intermediate-risk prostate cancer who received permanent seed brachytherapy at our center. Erectile function at baseline (prior to brachytherapy) was assessed using the Mount Sinai Erectile Function Score (MSEFS). Urinary symptoms at baseline and at 1 month and 4 months after brachytherapy were measured using the International Prostate Symptom Score (IPSS) questionnaire. Multiple linear regression, and a multivariable mixed linear model were used to analyze differences in IPSS from baseline to 1 month and 4 months after brachytherapy. Multiple logistic regression was used to investigate factors associated with normal erectile function at baseline.*

Results: *A total of 124 patients had data available for baseline, and 1 month and 4 months after brachytherapy. Having normal erectile function (MSEFS of 3) versus suboptimal erectile function (MSEFS 0 to 2) was not associated with increases in IPSS from baseline to 1 month or 4 months after brachytherapy. Larger increases in IPSS were found in subjects who had smaller prostates (regression coefficient = -0.36) or higher seed radioactivity (regression coefficient = 0.33). Patients with higher baseline IPSS were less likely to have normal erectile function (MSEFS = 3) before brachytherapy (odds ratio = 0.88).*

Conclusion: *Normal erectile function prior to brachytherapy was not associated with worse IPSS after brachytherapy. However, patients with a higher IPSS before brachytherapy also had worse erectile function before brachytherapy, which may point to a common pathway.*

Key Words: erectile function, prostate brachytherapy, urinary symptoms

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Introduction

There is an overlap between erectile function and lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH), pointing to a cause-and-

effect relationship.[1] The exact mechanism linking LUTS and erectile function, is not yet understood, although several different hypotheses have been proposed.[1-3]

In patients with prostate cancer, an association between erectile function and LUTS has, to the best of our knowledge, been reported in only one published study. That study reported an association in patients experiencing a flare up of urinary symptoms several months or years after prostate brachytherapy.[4] Interestingly, the most frequently used type of medication for erectile dysfunction (ED), phosphodiesterase type-5 inhibitors, is also effective in the treatment of LUTS, as shown in four randomized, placebo-controlled trials.[5-8] This suggests new explanations for the pathogenesis of ED and LUTS. Patients treated for prostate cancer, experience various degrees of LUTS and ED, and therefore, knowing more about the association between LUTS and ED, could be beneficial.

The aim of this study was to investigate whether a link exists between pretreatment erectile function and post treatment LUTS in prostate cancer patients who undergo permanent brachytherapy. Better understanding of any potential link between erectile function and LUTS could lead to the development of improved treatment strategies for patients who undergo brachytherapy.

Material and methods

We performed a retrospective analysis and analyzed data from 215 consecutive patients with prostate cancer who received permanent brachytherapy (radioactive seed implantation) monotherapy at a single center, between July 2005 and June 2008.

Most patients (80%) had low-risk prostate cancer, defined as a serum prostate-specific antigen (PSA) ≤ 10 ng/mL plus a biopsy sample with stage ≤ T2a cancer and a Gleason score ≤ 6. Another 20% of the patients had intermediate-risk prostate cancer. This was defined as either a serum PSA of 10 to 18 ng/mL and a Gleason score of 6 or a serum PSA < 10 ng/mL with a Gleason score of 7 (3+4) in a maximum of ≤ 33% of biopsies or stage T2b (3%). Another 3% of patients had stage T2b prostate cancer and were classified as intermediate-risk cancers.

All patients were treated with ^{125}I loose-seed-implants. The prescribed dose was 144 Gy. Seed activity ranged from 0.39 - 0.68 millicurie (mCi). The planning target volume (PTV) was the prostate gland plus a margin of 3 mm in all directions. Patients were treated with an intraoperative planning approach. Nine patients received neoadjuvant cytoreductive hormonal therapy prior to brachytherapy.

Brachytherapy technique

Brachytherapy was performed using a 3-D ultrasound-guided (BK Medical Systems, Herlev, Denmark) intraoperative interactive planning system with virtual needle guidance, robotic seed delivery, and needle retraction (FIRST, Nucletron®). Patients had a CT scan 30 days after the procedure to evaluate the implant quality and the radiation dose.

Measurements

Prior to brachytherapy, patients had their erectile function evaluated and graded according to the Mount Sinai Erection Function Score (MFEFS), where 0 = no erections; 1 = ability to have erections but insufficient erection for vaginal penetration; 2 = erectile function sufficient for vaginal penetration but suboptimal; and 3 = normal erectile function.[9]

The International Prostate Symptom Score (IPSS) was used to gauge LUTS—prior to brachytherapy, and at 1 month and 4 months after brachytherapy.

Statistical analyses

Multiple linear regression was performed to analyze differences in IPSS from baseline to 1 month and 4 months after brachytherapy. Multiple linear regression analysis and a multivariable mixed model[10] were used to determine which baseline characteristics were associated with significant increases in postbrachytherapy IPPS values (among subjects with the same baseline IPSS values). Independent continuous variables were age, prostate volume, baseline IPSS, seed activity (in mCi), number of seeds, number of needles, seeds per needle, activity (mCi) per cc of prostate volume, and patients in order of treatment. Binary variables included diabetes, cerebrovascular disease, use of hormonal therapy, and a baseline MSEFS of 3 versus a baseline MSEFS of 0-2. We performed sensitivity analyses to compare a baseline MSEFS of 2-3 versus a baseline MSEFS of 0-1.

Multiple logistic regression was used to investigate factors associated with a baseline MSEFS of 3 versus a baseline MSEFS of 0-2; and a baseline MSEFS of 2-3 versus a baseline MSEFS of 0-1. Independent continuous variables were age, prostate volume, and IPSS at baseline; binary variables included diabetes, cerebrovascular disease, and Gleason score (7 versus ≤ 6).

In all multivariable regression analyses, a 2-tailed $p < 0.05$ was used as a criterion for statistical significance of an independent association between an independent variable and an outcome, while adjusting for all other variables in the model. All analyses were performed with SAS statistical software (version 9.1; SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of the 215 study patients are shown in Table 1. A total of 189 patients had data for baseline erectile function. Of these patients, 8 patients had an MSEFS score of 0; 18 patients had a score of 1; 65 patients had a score of 3; and 98 patients had a score of 3 (normal erectile function). IPSS data at the 1 month follow up was available for 177 patients, and IPSS data at the 4 month follow up was available for 124 patients.

Table 2 lists the results from the linear regression analyses. Compared to having good pretreatment erectile function (MSEFS of 3), having suboptimal or absent erectile function (MSEFS of 0-2) was not independently associated with an increase in IPSS from baseline to 1 month after brachytherapy or 4 months after brachytherapy.

Having a small prostate volume was associated with a greater increase in IPSS 1 month after brachytherapy (regression coefficient = -0.38; 95%CI = -0.71 to -0.05). A one-unit increase in prostate volume was associated with, on average, a 0.38 point decrease in IPSS 1 month after brachytherapy. However, this significant

TABLE 1. **Clinical characteristics of study population (n = 215)**

Variable	**Mean (SD)**
Patient age (years)	65 (6.3)
PSA, ng/mL	6.2 (2.66)
Prostate volume (cc)	39 (9.7)
Number of seeds	62 (13.2)
Number of needles	24 (4.5)
Seed radioactivity (mCi)	0.52 (0.08)
Radioactivity/prostate volume (mCi/cc)	0.82 (0.12)
Seeds/needle	2.6 (0.33)
Variable	**%**
Gleason score 7	9.8
Use of hormonal therapy	4.5
Cerebrovascular disease	19.3
Diabetes	14.7

TABLE 2. **IPSS changes from baseline to 1 month or 4 months after permanent seed brachytherapy***

	IPSS changes from baseline to 1 month (n = 177)				**IPSS changes from baseline to 4 months (n = 124)**			
Variable	**Estimate**	**95% CI**		**p**	**Estimate**	**95% CI**		**p**
		Lower Limit	**Upper limit**			**Lower limit**	**Upper limit**	
Baseline IPSS	-0.56	-0.81	-0.31	< .0001	-0.48	-0.79	-0.16	0.0032
Prostate volume	-0.38	-0.71	-0.05	0.0234	-0.27	-0.65	0.10	0.1552
Order treated	0.01	-0.01	0.04	0.3817	0.01	-0.03	0.04	0.6394
Patient's age	-0.08	-0.24	0.07	0.286	-0.03	-0.19	0.13	0.7148
# needles	0.01	-1.46	1.48	0.9879	1.53	-0.01	3.07	0.0516
# seeds	0.40	-0.22	1.03	0.2035	-0.45	-1.13	0.23	0.1937
Seed activity	43.38	11.76	75.00	0.0075	11.92	-24.38	48.22	0.5164
Activity/cc	-5.47	-18.56	7.61	0.4098	-16.24	-31.51	-0.97	0.0373
Seeds/needle	0.31	-13.01	13.63	0.9634	14.96	0.13	29.78	0.048
Hormones	-0.72	-5.85	4.40	0.7807	-1.00	-11.57	9.57	0.8514
MSEFS 3 vs. 0-2	1.10	-0.89	3.08	0.2757	0.36	-1.87	2.60	0.7488
CV disease	1.63	-0.81	4.08	0.1893	0.75	-2.01	3.51	0.5906
Diabetes	-0.23	-2.93	2.47	0.8677	2.70	-0.29	5.69	0.0759

IPSS = International Prostate Symptom Score; MSEFS = Mount Sinai Erectile Function Score
*Multiple linear regression model

association with prostate volume was not found in the model for the change in IPSS at 4 months after brachytherapy.

Other factors associated with significantly larger increase in IPSS from baseline to 1 month after brachytherapy included: lower baseline IPSS (regression coefficient = -0.56; 95%CI = -0.81 to -0.31, per 1 point increase); greater radioactivity of seeds (regression coefficient = 0.43, 95%CI = 0.12 to 0.75, per 0.01 point increase).

Factors associated with significantly larger increase in IPSS from baseline to 4 months after brachytherapy included: lower baseline IPSS (regression coefficient = -0.48, 95%CI = -0.79 to -0.16, per 1 point increase); lower radioactivity per cc of prostate volume (regression coefficient =-0.16, 95%CI = -0.31 to -0.01, per 0.01 point increase); and greater number of seeds per needle (regression coefficient = 0.15, 95%CI = 0.13 to 0.30, per 0.01 point increase). Having brachytherapy done with a greater number of needles, and having diabetes were each associated with a marginally larger increase in IPSS from baseline to 4 months after brachytherapy. Similar results were obtained from the sensitivity analysis with a MSEFS of 2 to 3 versus a MSEFS of 0 to 1 (data not shown).

The multivariable mixed model analysis, Table 3, of the two combined postbrachytherapy IPSS values showed that IPPS decreased, on average, by 1.24 (95% CI = -2.31 to -0.16) from 1 month to 4 months after brachytherapy. Consistent with the findings from the multiple linear regression, erectile function (MSEFS 3 versus MSEFS 0 to 2) was not independently associated with postbrachytherapy increase in IPSS, and a larger prostate volume at baseline was associated with, on average, a 0.36 point decrease in postbrachytherapy IPSS (regression coefficient = -0.36; 95%CI: -0.65, -0.07 per 1 point increase). Higher radioactivity of seeds was associated with larger IPPS increases (regression coefficient = 0.33, 95%CI = 0.05 to 0.61 per 0.01 point increase). Higher radioactivity per cc of prostate volume was associated with marginally smaller increases in postbrachytherapy IPPS (regression coefficient = -0.10, 95%CI = -0.21 to 0.01 per 0.01 point increase).

In sensitivity analysis with the modified erectile function cut-off (2 to 32 versus 0 to 1), the same baseline characteristics were found to be statistically significant predictors of larger or smaller increases in postbrachytherapy IPPS scores (data not shown). Table 4 lists the results from the multiple logistic regression analysis to identify factors associated with erectile function before brachytherapy (at baseline), using two alternative cut-offs for MSEFS scores. The most important factor associated with normal

TABLE 3. **IPPS measurements at 1 and 4 months after brachytherapy (n = 124)***

Variable	Estimate	95% CI		p
		Lower limit	Upper limit	
Baseline IPSS	0.45	0.22	0.67	0.0001
Prostate Volume	-0.36	-0.65	-0.07	0.016
Order treated	0.01	-0.01	0.04	0.297
Age	-0.04	-0.18	0.09	0.5129
# needles	0.47	-0.79	1.72	0.4616
# seeds	0.14	-0.41	0.68	0.6179
Seed activity	33.18	5.09	61.28	0.0209
Activity/cc	-10.06	-21.43	1.31	0.0825
Seeds/needle	4.66	-6.93	16.25	0.4281
Hormones	-0.90	-5.74	3.95	0.7158
MSEFS (3 vs. 0-2)	0.58	-1.18	2.34	0.5158
CV disease	1.20	-0.96	3.36	0.2736
Diabetes	0.51	-1.89	2.90	0.6768
Month 4	-1.24	-2.31	-0.16	0.0242

IPSS = International Prostate Symptom Score; MSEFS = Mount Sinai Erectile Function Score
*Multiple linear regression model

TABLE 4. **Erectile function before brachytherapy***

Variable	MSEFS 3 vs MSEFS 0 to 2 (n = 95 vs n = 89)				MSEFS 2 to 3 vs MSEFS 0 to 1 (n = 158 vs n = 25)			
	OR	95% CI		Pr > ChiSq	OR	95% CI		Pr > ChiSq
		Lower limit	Upper limit			Lower limit	Upper limit	
Baseline IPSS*	0.88	0.80	0.96	0.0030	0.77	0.68	0.88	< .0001
Prostate volume	1.02	0.99	1.05	0.2787	1.05	0.99	1.10	0.1005
Age	0.95	0.90	1.00	0.0335	0.87	0.79	0.96	0.0055
CV disease	0.70	0.31	1.56	0.3788	0.52	0.18	1.53	0.2341
Diabetes	0.43	0.17	1.07	0.0701	0.22	0.07	0.70	0.0102
Gleason 7 vs 4-6	1.11	0.42	2.94	0.8372	4.35	0.51	37.27	0.1800

PSS = International Prostate Symptom Score; MSEFS = Mount Sinai Erectile Function Score
*Multiple linear regression model

erectile function (MSEFS score 3 versus 0-2) before brachytherapy is a lower IPSS at baseline (OR = 0.88, 95% CI = 0.80-0.96). A 1-point increase in baseline IPSS score was associated with a 12% decrease in the odds of having normal erectile function. Older patients had a significantly lower probability of normal erectile function (OR = 0.95 per 1 year increase in age, 95% CI = 0.90 to 1.00). The associations were stronger if patients with normal and suboptimal erectile function (MSEFS 3 and 2) are grouped together versus MSEFS of 0 and 1.

Discussion

Urinary symptoms are the most common side effects after brachytherapy.[11-13] Patients with LUTS are usually treated with alpha-blocker therapy and non-steroidal anti-inflammatory drugs, but some patients are still significantly bothered by symptoms.

We had observed that among patients who underwent brachytherapy at our center, compared to older patients, young patients with good erectile function before brachytherapy were more likely to develop worse LUTS after brachytherapy. The current study was designed to investigate the influence of erectile function on subsequent worsening of LUTS in patients treated with prostate brachytherapy

The study findings did not support our original clinical observation: prebrachytherapy MSEFS was not associated with worse LUTS after brachytherapy. However, low baseline MSEFS (no or suboptimal erections) was associated with high baseline LUTS. High baseline IPSS was also independently associated with a greater increase in IPSS at 1 month and 4 months after brachytherapy. This is, to our knowledge, the first evidence of an association between erectile function and LUTS at baseline among patients who underwent brachytherapy for prostate cancer.

The mechanism behind a possible association between erectile function and LUTS in patients undergoing brachytherapy for prostate cancer may involve a shared pathway. Elucidating the mechanism may lead to development of strategies to alleviate therapy-refractory LUTS following brachytherapy.

Four randomized clinical trials have found an association between LUTS and erectile function in patients with benign prostate hyperplasia (BPH), and have also found that when these patients were treated with a phosphodiesterase-type 5 (PDE-5) inhibitor, IPSS improved.[5-8]

Risk factors for LUTS are well documented. One factor regularly associated with an increase in urinary symptoms is a large pretreatment prostate volume.[11,13-16] This is in contrast to our results. We found that a larger prostate volume was associated with less urinary symptoms. This might be due to the fact that patients with prostate volumes > 50 cc—the volume generally associated with a higher incidence of urinary toxicity—were rarely (12%) treated in the present cohort. Otherwise, the risk factors for LUTS that we found in our study agreed with risk factors that have been described in other studies. The risk factors are diabetes[17] and the number of needles used.[11]

A possible interrelationship between LUTS and erectile function may be due to common pathways, etiologies, and risk factors. The link between LUTS

and erectile function may be related to four factors: 1) atherosclerosis results in loss of smooth muscle from the bladder detrusor, and prostate fibrosis; 2) atherosclerosis can lead to reduced nitric oxide levels; 3) autonomic hyperactivity (AH); or 4) Rho-kinase activation. All these mechanisms can affect muscle cell relaxation necessary for tumescence. An increased sympathetic muscle tone can increase BPH growth and LUTS, and vasoconstrictive forces that result in ED, and could implicate prostate and bladder neck smooth muscles.[1,2] ED is also associated with cardiac arteriosclerosis. Gazzaruso et al[18] found that ED, as measured with the International Index of Erectile Function -5 (IIEF-5), was associated with silent coronary artery disease (CAD), with which ED shares many risk factors. ED might be a harbinger of arteriosclerosis because the diameter of the arteries that supply the penis are in general smaller than the coronary arteries and ED might therefore predict risk of CAD.[19]

A possible limitation of the current study is that we did not use a standard patient-administered questionnaire, such as the IIEF-5, to evaluate erectile function. Instead, we used the physician-administered MSEFS. We chose the MSEFS because it is very easy to administer. Zagar et al[20] found a significant correlation between MSEFS and total IIEF-5 score. This coefficient was 0.65 for comparisons at initial patient consultations and was 0.76 in follow up visits. The IIEF-5 includes degree of sexual desire, while the MSEFS is simply based on erectile firmness.

A large, prospective study[21] in over 9000 men used a physician-applied scale that is very similar to the MSEFS, to grade erectile function and found that erectile function increased the risk of subsequent cardiovascular clinical events.

In conclusion, we found that patients with good erectile function have less LUTS before brachytherapy. We suggest that patients who undergo brachytherapy may be given a trial with a PDE5-I to evaluate its efficacy in treating and preventing urinary toxicity. □

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