Preoperative symptoms predict continence after post-radiation transurethral resection of prostate

Allison Polland, MD,[1] Emily A. Vertosick, MPH,[2] Daniel D. Sjoberg, MA,[2] Gillian L. Stearns, MD,[3] Laura S. Leddy, MD,[4] Marisa A. Kollmeier, MD,[5] Jaspreet S. Sandhu, MD[4]

[1]MedStar Washington Hospital Center, Washington, District of Columbia, USA
[2]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York, USA
[3]University of Vermont Medical Center, Burlington, Vermont, USA
[4]Department of Surgery, Urology Service, Memorial Sloan-Kettering Cancer Center, New York, New York, USA
[5]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

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Introduction: *Lower urinary tract symptoms and retention are known complications of radiation for prostate cancer and traditionally transurethral resection of the prostate (TURP) has been avoided in these patients because of the risk of incontinence. The purpose of this study was to evaluate the incidence and predictors of post-TURP incontinence in previously radiated patients.*
Materials and methods: *One-hundred and eleven patients who underwent brachytherapy or external beam radiotherapy for prostate cancer with subsequent TURP performed between 1992 and 2012 at a single institution were identified. We tested for associations between post-TURP continence status and pre-TURP predictors including age, preoperative urinary symptoms and type and timing of radiation therapy.*
Results: *New-onset incontinence developed in 27% (95% CI 17%, 39%) of patients after first post-radiation TURP and 32% (95% CI 23%, 42%) of patients after any TURP, including repeat TURPs. Forty-three percent of patients had resolution of incontinence with first TURP (95% CI 25%, 63%); only 25% (95% CI 7%, 52%) of patients had resolution following repeat TURPs. Age was significantly associated with incontinence (OR per 10 years 2.02, 95% CI 1.10, 3.74, p = 0.024). Post-TURP incontinence was more common in men with pre-TURP urgency.*
Conclusions: *Rates of post-TURP incontinence were higher in men who were older or had pre-TURP urinary urgency. Assessment of preoperative symptoms would allow for better patient selection. Further research should determine whether this results in better outcomes, including decreased incidence of new onset incontinence and increase in resolution of incontinence.*

Key Words: transurethral resection of prostate, prostate cancer, radiation, incontinence, urgency

Introduction

Transurethral resection of the prostate (TURP) is a common treatment for obstructive urinary symptoms and acute urinary retention. In patients with pure obstruction, TURP results in improved voiding, whereas in patients with detrusor overactivity it may result in unobstructed passage of urine with unstable contractions. TURP carries a risk of urinary incontinence which is often thought to occur due to injury of the external sphincter. The risk of urinary incontinence after TURP for benign prostatic hypertrophy is approximately 1%-5%.[1,2]

Lower urinary tract symptoms (LUTS) and urinary retention are known complications of prostate radiation therapy, both external beam radiotherapy (EBRT) and brachytherapy. While these symptoms are usually temporary, patients with persistent LUTS or urinary retention present a diagnostic and treatment challenge.[3] TURP in these patients is widely

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Address correspondence to Dr. Allison Polland, MedStar Washington Hospital Center, 110 Irving Street NW, Washington, DC 20010 USA

assumed to be more morbid than in patients without prior radiation. Several studies have documented increased rates of incontinence, up to 70%, in patients undergoing TURP after brachytherapy[4-8] as well as after EBRT.[9-11] These studies have not examined the preoperative symptoms for which patients underwent TURP, something that may influence postoperative incontinence. The purpose of this study was to evaluate the incidence of post-TURP incontinence in previously radiated patients and determine predictors of urinary continence.

Materials and methods

After IRB approval, 111 patients who underwent brachytherapy or external beam radiotherapy for prostate cancer with subsequent TURP performed between 1992 and 2012 at a single institution were identified. All TURPs were performed via electrosurgical resection. Urinary symptoms were recorded before and after TURPs. Urinary urgency and incontinence were determined by asking patients specifically about the presence or absence of these symptoms. Post-TURP symptoms were assessed at visits between 6 months and 1 year after surgery to allow for resolution of immediate postoperative symptoms, with continence being a patient-reported binary endpoint. Urinary incontinence was defined as any degree of uncontrolled leakage of urine. Patients were excluded if TURP was performed as part of a transurethral resection of a bladder tumor, or for a purpose other than relief of lower urinary tract symptoms, such as unroofing of prostatic abscess. Of the original cohort, 101 patients remained after excluding ineligible patients (n = 5) and those missing data on continence before or after TURP (n = 5). Of these patients, 101 patients had at least one post-radiation TURP, 34 patients had two post-radiation TURPs, and 12 patients had three or more post-radiation TURPs, for a total of 147 TURPs. Patients in this cohort were not limited by when the TURP was performed or when radiation therapy was received.

We aimed to assess whether there was an association between continence after a patient's first TURP and the following pre-TURP predictors among all patients and among previously-continent patients: pre-TURP retention; pre-TURP urgency; type of radiation; time from end of radiation therapy to TURP; age at TURP; number of previous TURPs; and decade in which radiation therapy was performed. We created separate logistic regression models to test for association between each predictor and post-TURP continence, adjusting for pre-TURP continence. Since there were several patients who had had multiple post-radiation TURPs, a generalized estimating equation (GEE) model (assuming an exchangeable correlation structure) was used to assess whether each of these predictors was associated with a change in continence after any TURP procedure. Separate GEE models were created for each predictor and were adjusted for pre-TURP continence. All analyses were conducted using Stata 12.0 (Stata Corp., College Station, TX, USA).

Results

Forty-seven percent of patients were in retention prior to TURP, Table 1. Out of the 101 patients, 70 (69%) were continent before their first post-radiation TURP.

TABLE 1. **Patient characteristics, n = 101. Data are given as median (IQR) or frequency (%)**

Age at radiation therapy (n = 89)	66 (60, 71)
Age at TURP (years) (n = 94)	74 (68, 80)
Type of radiation (n = 93)	
Brachytherapy	19 (20%)
EBRT	58 (62%)
Combination brachytherapy/EBRT	16 (17%)
Pre-treatment hormone therapy (n = 64)	36 (56%)
Post-treatment hormone therapy (n = 64)	50 (78%)
Clinical T stage (n = 81)	
T1	30 (37%)
T2	36 (44%)
T3	11 (14%)
T4	4 (5%)
Biopsy Gleason score (n = 84)	
<=6	32 (38%)
7	27 (32%)
8	14 (17%)
9-10	11 (13%)
Patient had pre-radiation TURP (n = 87)	5 (6%)
Pre-TURP symptoms	
Incontinence	29 (29%)
Urgency	40 (40%)
Retention	47 (47%)
Post-TURP incontinence	36 (36%)
Time between radiation and first TURP (years) (n = 91)	7.0 (3.8, 11.0)

TURP = transurethral resection of the prostate
EBRT = external beam radiotherapy

TABLE 2. **Rates of post-TURP continence, by pre-TURP continence and urgency**

	No urgency	Urgency	Risk difference (95% CI)	p value
Pre-TURP continence	53 (74%)	15 (54%)	20% (-1.1%, 41%)	0.054
Pre-TURP incontinence	4 (36%)	12 (36%)	0% (-33%, 33%)	> 0.9

TURP = transurethral resection of the prostate

Of these 70, 19 patients developed incontinence after the first post-radiation TURP (27%, 95% CI 17%, 39%). Including repeat TURPs, 100 of the total 147 TURPs were performed on patients who were continent before the procedure. Of these 100 procedures, 32 resulted in post-TURP incontinence (32%, 95% CI 23%, 42%).

A number of patients in the cohort had some degree of stress, urge or overflow incontinence before TURP. Patients who were incontinent before their first post-radiation TURP were more likely to be incontinent after TURP when compared to men who were continent pre-TURP (57% versus 27%, risk difference 30%, 95% CI 9%, 51%, p = 0.005). The same association was seen when including all 147 TURPs: 64% of previously-incontinent men remained incontinent, while only 32% of previously-continent men became incontinent after the procedure (risk difference 32%, 95% CI 15%, 49% p = 0.0004). Of the 28 patients who were incontinent before their first TURP, 12 had resolution of their incontinence after the procedure (43%, 95% CI 25%, 63%). Sixteen repeat TURPs were performed on men who were incontinent, with incontinence resolving in only four cases (25%, 95% CI 7%, 52%). Although a greater proportion of patients had resolution of incontinence with first TURP as compared to repeat TURP, the difference between these two groups was not significant (risk difference 18%, 95% CI -10%, 46%, p = 0.2).

In this cohort, men who were continent with urgency symptoms pre-TURP appeared to be more likely to become incontinent after TURP. There were 61 cases in which patients had pre-TURP urgency (42%) and 83 cases (58%) without urgency. Of the 83 cases in which patients had no urgency, 72 were continent before surgery and only 19 (26%) became incontinent, Table 2. In comparison, about half of previously-continent men with urgency symptoms (13 out of 28 men in this cohort) became incontinent after TURP (risk difference 20%, 95% CI -1.1%, 41%, p = 0.054).

However, pre-TURP urgency symptoms did not seem to affect post-TURP continence in men who were incontinent before their TURP procedure. About two-thirds of incontinent men remained incontinent after TURP, regardless of pre-TURP urgency symptoms. While the association between pre-TURP urgency and post-TURP continence in previously-continent patients did not reach conventional levels of statistical significance when adjusted for pre-TURP incontinence (OR 2.24, 95% CI 0.91, 5.54, p = 0.081, Table 3a), the odds ratio was consistent with the findings that continent men with urgency in this cohort had considerably higher chance of becoming incontinent after TURP than continent men without urgency symptoms. Pre-TURP retention was not found to be a significant predictor of post-TURP incontinence.

When testing for associations between pre-TURP characteristics and post-TURP incontinence for TURPs among previously-continent men, age was found to be significantly associated with incontinence (OR per 10 years 2.02, 95% CI 1.10, 3.74, p = 0.024); age was also associated with time between radiation and first TURP. Time between radiation therapy and TURP was also found to influence post-TURP continence (OR per 10 years 2.30, 95% CI 0.91, 5.81, p = 0.078, Table 3a). Since time between radiation and TURP may be correlated with the decade in which radiation therapy was received, the association between time between radiation and TURP when adjusting for decade of radiation was assessed. There was no significant association between time between radiation and TURP and post-TURP continence (OR per 10 years = 2.38, 95% CI 0.69, 8.26, p = 0.2).

The majority of patients (79%) received EBRT, whether alone or in combination with brachytherapy. Sixty-three percent of patients also received hormonal therapy at some point, whether it was before or after radiation treatment. In this cohort, among men with a history of brachytherapy (35/101 men, 35%), more men became incontinent and fewer previously-incontinent men became continent after TURP when compared to men who had EBRT alone, although the difference was not statistically significant, Table 4. A summary of the association between post-TURP continence status and the pre-TURP predictors when adjusting for pre-TURP incontinence is shown in Tables 3a and 3b.

TABLE 3a. **Univariate general estimating equation for the association between post-TURP continence status and pre-TURP predictors for all TURPs among continent patients (70 patients, 100 TURPs)**

	OR	95% CI	p value
Retention	1.50	0.64, 3.56	0.4
Urgency	2.24	0.91, 5.54	0.081
LUTS NOS	0.55	0.19, 1.54	0.3
Retention or BOO	1.17	0.48, 2.86	0.7
Time from radiation to TURP (per 10 years)	2.30	0.91, 5.81	0.078
Age at TURP (by 10 years)	2.02	1.10, 3.74	0.024
Number of post-radiation TURP	1.01	0.61, 1.65	> 0.9
Type of radiation			
EBRT (Ref.)	1.00	-	-
Brachytherapy	2.28	0.84, 6.18	0.11
EBRT & brachytherapy	1.02	0.28, 3.73	> 0.9
History of brachytherapy	1.73	0.72, 4.15	0.2
Decade of radiation			
1980s (Ref.)	1.00	-	-
1990s	1.01	0.17, 5.86	> 0.9
2000s	0.94	0.15, 5.80	0.9
Year of first TURP			
Pre-2000 (Ref.)	1.00	-	-
2000-2005	2.26	0.31, 16.71	0.4
2006-2012	3.09	0.42, 22.95	0.3

TURP = transurethral resection of the prostate; LUTS = lower urinary tract symptoms; NOS = not otherwise specified; BOO = bladder outlet obstruction; EBRT = external beam radiotherapy

TABLE 3b. **Univariate logistic regression for the association between post-TURP continence status and pre-TURP predictors for first TURP among continent patients (70 patients, 70 TURPs)**

	OR	95% CI	p value
Retention	1.43	0.49, 4.14	0.5
Urgency	1.90	0.61, 5.90	0.3
LUTS NOS	0.70	0.20, 2.49	0.6
Retention or BOO	1.02	0.34, 3.03	> 0.9
Time from radiation to TURP (per 10 years)	1.90	0.66, 5.51	0.2
Age at TURP (by 10 years)	2.27	0.99, 5.21	0.053
Type of radiation			
EBRT (Ref.)	1.00	-	-
Brachytherapy	2.50	0.69, 9.12	0.2
EBRT & brachytherapy	2.67	0.59, 12.09	0.2
History of brachytherapy	2.56	0.84, 7.79	0.1
Decade of radiation			
1980s (Ref)	1.00	-	-
1990s	1.14	0.10, 12.66	0.9
2000s	2.25	0.20, 25.37	0.5

TURP = transurethral resection of the prostate; LUTS = lower urinary tract symptoms; NOS = not otherwise specified; BOO = bladder outlet obstruction; EBRT = external beam radiotherapy

TABLE 4. **Rates of post-TURP continence, by pre-TURP continence and history of brachytherapy**

	No brachytherapy	Brachytherapy	Risk difference (95% CI)	p value
Pre-TURP continence	38 (70%)	18 (56%)	14% (-7%, 35%)	0.2
Pre-TURP incontinence	9 (43%)	6 (29%)	14% (-14%, 43%)	0.3

TURP = transurethral resection of the prostate

Discussion

While LUTS after radiation are common, the majority of symptoms resolve spontaneously. However in up to 18% of cases, symptoms fail to resolve and patients require surgical intervention.[12] TURP in these patients has traditionally been thought to cause significant morbidity, specifically incontinence. Urinary incontinence is not a single entity but rather has multiple subtypes with varying causes classified based on symptomatology. Stress urinary incontinence (SUI) is the episodic loss of urine due to increased abdominal pressure during coughing, sneezing, straining or exercise. SUI may have varying underlying causes including intrinsic sphincter deficiency which may occur with inadvertent damage to the external urinary sphincter during TURP, overflow and detrusor overactivity in which stress triggers an involuntary contraction. Urge urinary incontinence (UUI) is a sense of urgency with loss of urine. This may be due to detrusor overactivity; however, low bladder compliance, urinary retention, and irritation due to urinary tract infection may cause it as well. Mixed urinary incontinence is a combination of stress and urge urinary incontinence.[13]

In the current study, previously-continent patients with urgency appeared to have a higher risk of post-TURP incontinence than previously-continent patients without urgency. Almost half of the continent patients with pre-TURP urgency developed incontinence after surgery. Based on symptomatology of urgency, these patients likely had a component of detrusor overactivity. TURP, by reducing the bladder outlet obstruction, may have allowed for urine leakage in response to overactive contractions leading to incontinence. Mock and colleagues found UUI more common than SUI after post-radiation TURP, consistent with the current findings.[6]

Men who were incontinent before their first TURP had a higher risk of incontinence after the procedure compared with men who were continent. Some men, however, had resolution of incontinence after TURP. In these patients, incontinence may have been due to overflow which was relieved with removal of obstructing prostatic tissue. Resolution of incontinence was seen in 43% of patients who were incontinent before their first TURP, while incontinence resolved after repeat TURPs in only 25% of cases. Although there were not enough cases to show a significant difference in resolved incontinence between first and repeat TURPs, a greater percentage of patients had resolution of incontinence with first TURP. Since initial TURP may have removed obstructing tissue, patients who remained incontinent after first TURP may have had a cause of incontinence other than overflow, such as detrusor overactivity, and therefore were less likely to have resolution of incontinence upon repeat TURP.

In the current series, 27% of patients developed incontinence after first TURP. Of the 31 men who underwent multiple TURPs in this series, 23 remained continent after first TURP and 10 remained continent after all subsequent TURPs. The remaining 13 men (42%) became incontinent after any subsequent TURP. Varying rates of incontinence have been reported after post-radiation TURP with a lower incidence of incontinence in those series with short follow up.[8,10] In contrast, Kollmeier and colleagues report incontinence in 18% of patients after post-brachytherapy TURP at a median follow up of 38 months,[7] while Mock and colleagues using the same series of patients found 25.3% developed incontinence by 7.2 years.[6] In that series, of the 15 patients who required multiple TURPs, 8 (53%) developed incontinence. In the current series, there was no significant difference in the development of incontinence between first TURP and repeat TURP groups.

Controversy exists regarding the optimal time to perform TURP after radiation, as acute post-treatment symptoms often resolve within 1 to 2 years.[14] Some series have reported that shorter time from external beam radiation therapy to TURP correlates with a higher risk of incontinence.[11] Kollmeier and colleagues suggested the opposite conclusion, with increased incontinence in patients who underwent TURP more

than 2 years following brachytherapy.[7] Mock and colleagues, using the same data set but with a greater number of patients and longer follow up, found no correlation between time to TURP and incontinence.[6] This is consistent with this series in which there was no significant correlation between time between radiation and TURP and incontinence.

Age was significantly associated with incontinence in this study, and remained significant when accounting for decade of radiation. Decade of radiation approached significance on univariate analysis but not when adjusting for time between radiation and TURP. This loss of significance suggests that time between radiation and TURP may be a proxy for decade of radiation treatment; those patients who have at least 10 years between radiation and TURP underwent radiation in the early 2000s, those with 20 years in the 1990s, and those with 30 years in the 1980s. In the modern era central urethral dose with brachytherapy has been limited, as TRUS and real-time, peripherally loaded technique allow for flexibility in seed positioning, and immediate adjustment and fine-tuning based on the isodose curves.[7] Developments in EBRT such as three-dimensional conformal therapy and more importantly intensity-modulated radiotherapy have allowed for delivery of the intended radiation dose to the target area while limiting irradiation of surrounding structures.[15] With these improvements, one might expect that decade of radiation affects development of fibrosis and thereby incontinence. This however was not the case in the current series which suggests that the relationship between radiation and fibrosis may be more complex. An explanation postulated by Hall and colleagues suggests that obstructive symptoms which develop years after prostate radiation may be due to a genetic susceptibility to radiation-induced fibrosis which they found to be more common in carriers of mutations in the ataxia-telangiectasia gene.[16]

LUTS are generally difficult to study quantitatively, particularly when incontinence rates are also high. While there are a number of validated questionnaires such as the IPSS, these may be difficult to interpret in the post-radiation setting where patients may have symptoms related to inflammation from the radiation itself, progression of the cancer or radiation-induced fibrosis. Kollmeier and colleagues reported a mean change in IPSS of -0.1 in those patients who developed incontinence and of +2 in those patients who did not develop incontinence.[7] Small changes like this in IPSS are difficult to interpret clinically. Urodynamic testing may be valuable in determining the underlying cause of the symptoms. Further research with urodynamic assessment would be helpful in better understanding the association between pre-TURP voiding dysfunction and post-TURP incontinence. Many practicing urologists do not perform urodynamic studies prior to TURP and therefore use clinical symptoms alone in making treatment decisions. Evaluation of the presence or absence of urgency could be a valuable addition to preoperative assessment prior to TURP in post-radiation patients. The current study does not address medical intervention prior to TURP, the availability of which varied over the study period. Still the importance of assessing urinary symptoms, whether with or without medical therapy, prior to surgery cannot be understated. All TURPs were performed via electrosurgical resection in the current study, the results therefore may not be generalizable to patients who undergo photovaporization or other procedures for obstructive symptoms.

Conclusion

LUTS often develop in patients after radiation for prostate cancer. The traditional approach has been to avoid TURP in these patients because of a risk of incontinence. Among previously-continent men in this cohort, rates of post-TURP incontinence were higher in men who were older or had pre-TURP urinary urgency. Therefore assessment of preoperative symptoms allows for better patient selection resulting in better outcomes, including decreased incidence of new onset incontinence and increase in resolution of incontinence. □

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