## Title
Urethroplasty After Radiation Therapy for Prostate Cancer



**Journal**
Urology, 79(6)

**ISSN**
0090-4295

**Authors**
Glass, Allison S
McAninch, Jack W
Zaid, Uwais B
et al.

**Publication Date**
2012-06-01

**DOI**
10.1016/j.urology.2011.11.077

Peer reviewed

# Urethroplasty After Radiation Therapy for Prostate Cancer

**Allison S. Glass, Jack W. McAninch, Uwais B. Zaid, Nadya M. Cinman, and Benjamin N. Breyer**

**OBJECTIVE** To report urethroplasty outcomes in men who developed urethral stricture after undergoing radiation therapy for prostate cancer.

**METHODS** Our urethroplasty database was reviewed for cases of urethral stricture after radiation therapy for prostate cancer between June 2004 and May 2010. Patient demographics, prostate cancer therapy type, stricture length and location, and type of urethroplasty were obtained. All patients received clinical evaluation, including imaging studies post procedure. Treatment success was defined as no need for repeat surgical intervention.

**RESULTS** Twenty-nine patients underwent urethroplasty for radiation-induced stricture. Previous radiation therapy included external beam radiotherapy (EBRT), radical prostatectomy (RP)/EBRT, EBRT/brachytherapy (BT) and BT alone in 11 (38%), 7 (24%), 7 (24%), and 4 (14%) patients, respectively. Mean age was 69 (±6.9) years. Mean stricture length was 2.6 (±1.6) cm. Anastomotic urethroplasty was performed in 76% patients, buccal mucosal graft in 17%, and perineal flap repair in 7%. Stricture was localized to bulbar urethra in 12 (41%), membranous in 12 (41%), vesicourethra in 3 (10%), and pan-urethral in 2 (7%) patients. Overall success rate was 90%. Median follow-up was 40 months (range 12-83). Time to recurrence ranged from 6-16 months.

**CONCLUSION** Multiple forms of urethroplasty appear to be viable options in treating radiation-induced urethral stricture. Future studies are needed to examine the durability of repairs. UROLOGY 79: 1402–1406, 2012. © 2012 Elsevier Inc.

Pelvic radiation is a frequently used treatment strategy for localized prostate cancer. External beam radiotherapy (EBRT), either as primary or adjuvant to radical prostatectomy (RP), and brachytherapy (BT) are effective treatment modalities.[1-3] EBRT involves directing gamma radiation to the prostate and surrounding tissues, usually in doses of 70-80 Gy.[4] Likewise, BT involves implantation of radioactive seeds or needles into the prostate gland to deliver high-dose radiation while sparing nearby tissues.[4] In high-risk patients, BT may be combined with EBRT to maximize radiation dose to prostate.

Radiation toxicity is common and can limit treatment dose or duration.[5] One-third of patients will experience acute bowel or urinary symptoms and up to 10% have permanent complications.[4] Radiation therapy causes vascular damage, ischemia, and fibrosis, contributing to urethral stricture disease.[6] Reported incidence of radiation-induced urethral stricture is variable. For patients who underwent EBRT and BT, stricture has been reported in 1.7% and 1.8% of patients respectively, whereas 5.2% of patients developed stricture after combined therapy.[7] Mohammed et al reported an incidence of 11% of ≥grade 2 and 10% of ≥grade 3 toxicity in patients who received a combination EBRT and high-dose-rate BT.[8] Sullivan et al similarly reported a higher rate of 12% for combined therapy.[9]

Anastomotic urethroplasty is a cost-effective, durable treatment for urethral stricture disease.[10] Other repair types, such as buccal mucosal onlay graft, penile flap, and perineal flap, have also been successful for urethral stricture disease.[11-13] Little literature exists on the outcomes of urethroplasty for radiation-induced urethral stricture. Recent studies describe success in more than two-thirds of patients.[14,15] Our objective is to report outcomes of urethroplasty performed after radiation therapy for prostate cancer.

## MATERIAL AND METHODS

### Patient Population

Patient data was collected after approval was obtained from the local institutional review board. All urethroplasties performed between June 2004 and May 2010 by a single surgeon were reviewed. Twenty-nine patients underwent urethroplasty for radiation-induced stricture disease. Study inclusion criteria involved any patient who underwent urethroplasty for radiation-induced stricture secondary to pelvic radiation for prostate

**Financial Disclosure:** *The authors declare that they have no relevant financial interests.*

*From the Department of Urology, University of California, San Francisco, San Francisco General Hospital, San Francisco, California*

*Reprint requests: Dr. Jack W. McAninch, Department of Urology, University of California, San Francisco, San Francisco General Hospital, 1001 Potrero Avenue Suite 3A, San Francisco, CA 94117. E-mail: jmcaninch@urology.ucsf.edu*

*Submitted: October 7, 2011, accepted (with revisions): November 19, 2011*

  0090-4295/12/$36.00
doi:10.1016/j.urology.2011.11.077

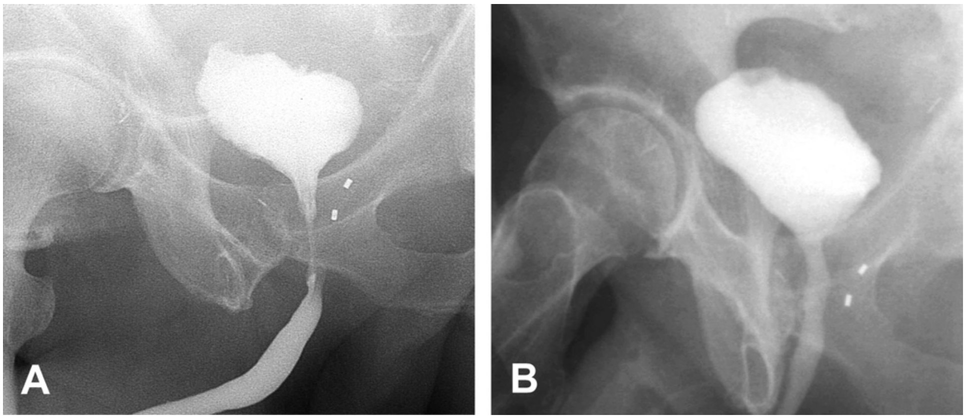


**Figure 1.** Retrograde urethrogram demonstrating high-grade posterior urethral stricture **(A)** and resolution of stricture after anastomotic urethroplasty **(B)**.

cancer. Forms of urethroplasty used were primary anastomosis, buccal graft urethroplasty, penile flap, or perineal flap urethroplasty. Five patients were noted to have stricture-associated rectourethral fistula. Fistula repair was performed in conjunction with urethroplasty in these patients. Patients were excluded if prostate cancer therapy did not include pelvic radiation (i.e. EBRT, BT, or combined).

All patients underwent intraoperative sonourethrogram to confirm the length and location of the urethral stricture. Patients with anterior stricture disease were managed with either anastomotic urethroplasty or buccal mucosal graft, or penile flap. The decision to use buccal mucosa onlay graft was made by a single surgeon on a case-by-case basis and when anastomotic urethroplasty was not feasible (typically >2.5-cm length).

Stricture-related variables included length, location, prior urethral stricture surgery (direct vision internal urethrotomy [DVIU], dilation, urethroplasty), and type of urethroplasty performed (anastomotic, buccal mucosal graft onlay, penile flap, perineal graft). Specific medical comorbidities documented in preoperative history were included in patient evaluation. These included presence or absence of tobacco use (ie, any use of cigarettes within 1 month of surgery), diabetes mellitus, hypertension, and dyslipidemia. Descriptive statistics were used to characterize the study population. Chi-square test was used to compare groups and determine statistical significance. Statistical significance was set at $P < .05$ and all tests were 2-sided. Stata 11 (StataCorp, College Station, TX) was used for all analyses.

### Follow-Up

All patients were clinically evaluated within 3 months after undergoing urethroplasty. A voiding cystogram was performed at catheter removal, and both a retrograde urethrogram and voiding cystogram were performed during follow-up at 3 months and 1 year (Fig. 1). Additional fluoroscopic images were obtained if subjective obstructive symptoms were present. In addition, further fluoroscopic imaging was obtained when peak urinary flow decreased to <15 mL/s or a change in voiding pattern was seen on uroflowmetry during other follow-up visits.[16] Subsequent follow-up was noted when present and included follow-up telephone conversations. Stricture recurrence was defined as the presence of obstructive voiding symptoms and/or the need for further urethral intervention.

**Table 1.** Cohort features

| | |
|---|---|
| Radiation type, n (%) | |
| EBRT | 11 (38) |
| EBRT/RP | 7 (24) |
| EBRT/BT | 7 (24) |
| BT | 4 (14) |
| Location of stricture, n (%) | |
| Bulbar | 12 (41) |
| Membranous | 12 (41) |
| Vesicourethral | 3 (10) |
| Pan-urethral | 2 (7) |
| Prior treatment, n (%) | |
| Dilation | 10 (34) |
| DVIU | 8 (28) |
| AUS | 3 (10) |
| Urethroplasty | 1 (3) |
| UroLume stent | 1 (3) |

EBRT = external beam radiotherapy, RP = retropubic prostatectomy, BT = brachytherapy, DVIU = direct vision internal urethrotomy, AUS = artificial urinary sphincter.

## RESULTS

Twenty-nine men underwent urethroplasty for radiation-induced urethral stricture disease over a 6-year period. The mean age was 69 years (SD ±6.9). Stricture-treatment modalities received before urethroplasty included DVIU (28%), dilation (34%), artificial urinary sphincter (AUS) placement (10%), urethroplasty (3%), and UroLume stent (3%) (AMS, Minnetonka, MN). Prostate cancer therapies included EBRT (38%), RP/EBRT (24%), EBRT/BT (24%), and BT (14%) (Table 1).

Mean time from radiation exposure to stricture development and presentation to our center was 7 ± 3.8 years. Mean stricture length was 2.6 ± 1.6 cm. Stricture was localized to bulbar urethra in 41% patients, membranous 41%, vesicourethra 10%, and pan-urethral in 7%. Forty-eight percent of patients had a known history of hypertension. Other documented comorbidities included dyslipidemia (31%), coronary artery disease (17%), diabetes (14%), and recent tobacco use (7%).

Anastomotic urethroplasty was the most commonly used procedure (76%) followed by buccal mucosal graft

**Table 2.** Results

| | |
|---|---|
| Repair type, n (%) | |
| Anastomotic | 22 (76) |
| Buccal | 5 (17) |
| Perineal flap | 2 (7) |
| Complications, n (%) | |
| Urge incontinence | 2 (7) |
| Wound infection | 1 (3) |
| Failure type, n (%) | |
| Anastomotic | 1 (3) |
| Buccal | 1 (3) |
| Perineal flap | 1 (3) |

(17%), and perineal flap repair (7%). Five patients (17%) had stricture-associated rectourethral fistula. Mean fistula length was 2.25 ± 0.25 cm. Three were localized to prostatic urethra, 1 in membranous, and 1 in the bladder neck. Median length of follow-up was 40 months (range 12-83*). The overall success rate was 90%. Three (10%) patients had stricture recurrence with median time to recurrence of 12 months. Comorbidity data of the 3 patients who failed treatment included history of hypertension and dyslipidemia. Of these, one patient underwent buccal urethroplasty for bulbourethral stricture and ultimately underwent urinary diversion. The second patient, also with bulbourethral disease, underwent anastomotic repair. The third patient had a pan-urethral stricture treated with perineal flap. The latter patients required DVIU and dilation, respectively. Postprocedure complications included necrotizing wound infection in 1 patient. Two patients (7%) developed new urge incontinence, one of whom ultimately required AUS placement (Table 2). Previous surgery had little effect on overall outcome. Those who underwent RP in addition to EBRT had slightly lower success rates compared with the rest of the cohort (86%, 6/7 vs 91%, 20/22; $P = .694$). In addition, men who have had previous urethral surgery also had a slightly lower success rate (88%, 15/17 vs 92%, 11/12; $P = .765$). We stratified success rates by radiation type and found minor differences that were not statistically significant. The success rates for EBRT, RP/EBRT, EBRT/BT, and BT were 82%, 86%, 100%, and 100%, respectively ($P = .549$).

## COMMENT

Management of localized prostate cancer typically involves active surveillance, pelvic radiation, or surgical removal. The damaging effects of radiation therapy are apparent as the association between urethral stricture disease and prostate cancer therapy is well established. The effects of radiation induce an obliterative endarteritis that results in ischemia and fibrosis of the irradiated tissue. Although single-modality radiation is associated with a lower risk of urethral stricture (1.7-4%), combination radiotherapy is associated with a 5.2-12% incidence of urethral stricture formation.[7-9]

Compromised wound healing, altered tissue planes, and impaired blood supply of irradiated tissue can contribute to urethroplasty failure. Stricture recurred in 10% of this cohort, which is lower than the reported rate of 27-29% in similar studies.[14-15,17] Factors that can contribute to the failure of urethroplasty include complex nature of the stricture, difficult location, or pronounced tissue damage secondary to radiation.[18] The effects of pelvic irradiation, including ischemia and fibrosis, affect the entire surgical field, potentially compromising the success of repair.[14] Patient history of microvascular disease likely contributes to urethroplasty failure. All three patients who developed stricture recurrence had a known history of hypertension and dyslipidemia. Similarly, tobacco use has been directly associated with urethroplasty failure, but not necessarily in urethral stricture development.[17]

Onset of subacute and chronic complications after radiation therapy occurs at approximately 6-24 months. Chronic complications, such as bleeding, fibrosis, and scarring can arise decades after radiation.[6] In our cohort, patients presented with urethral stricture at a mean of 84 months after radiation.

It is unclear how current advances in radiation, including conformal treatment of the prostate, will affect complication patterns. Although the morbidity involving other organs, such as radiation cystitis and proctitis may be reduced, the bleeding and fibrosis of the targeted prostate may not reduce prostatic or urethral complications. Sullivan et al report a 12% incidence of ≥grade 2 urinary complications at a 6-year follow-up evaluation in a cohort of 474 patients who underwent high-dose radiation therapy for prostate cancer.[9] The area of the urethra identified with a stricture post–high-dose radiotherapy was the bulbomembranous urethra, which exceeded the rates of stricture formation at the bladder neck or prostatic urethra. Risk for bulbomembranous urethral stricture development was higher in patients with a history of transurethral resection of the prostate (TURP), hypertension, those treated with high-dose radiation monotherapy without a boost, and those with increasingly high doses of more concentrated brachytherapy.

With high-dose brachytherapy, age at treatment, prostate-specific antigen, Gleason score, stage, risk category, smoking history, vascular event history, diabetes presence, androgen deprivation use, the duration of urethral catheterization, and total radiation dose were not identified to be associated with urethral stricture development.[9] Reports of urethral stricture development after radiotherapy for prostate cancer generally identify strictures that result in symptoms, so there may be an underestimation in the true rate of urethral stricture development.

Before urethroplasty, patients typically undergo minor surgical attempts to repair urethral stricture. One-third of patients in this cohort underwent either DIVU (28%) or dilation (34%). It has been established that prior history

*One patient died of unrelated causes 2 months after undergoing urethroplasty and therefore follow-up time could not be included.*

of stricture treatment contributes to urethroplasty failure.[17,19-20] Two of the patients who failed urethroplasty (67%) had a history of treatment attempts in the form of dilations, DVIU, and UroLume stent. Inflammation from prior instrumentation is superimposed on irradiated tissue, likely contributing to urethroplasty failure in these patients. Treatment failure was successfully managed with dilation (33%), DVIU (33%), and urinary diversion (33%). One patient developed stricture likely in part because of prior incontinence surgery. After undergoing RP and adjuvant EBRT, the patient developed severe incontinence. An AUS was placed and after a few years the AUS was replaced with a double-cuff after the patient experienced incontinence recurrence. The patient's incontinence persisted after the double-cuff, so in addition, a urethral sling was placed. The patient then developed a long obliterated bulbar stricture. After urethral reconstruction and removal of all prosthetics, another AUS was placed and is now functioning well.

Other postprocedure complications encountered in this cohort include new urge incontinence (7%), which was persisted in one patient who ultimately underwent placement of an AUS. Incontinence after urethroplasty for radiation-induced stricture disease is reported to be as high as 50%.[14]

Limitations of this study included its relatively small cohort size and short follow-up time. There was unequal distribution of urethroplasty type (24% underwent non-anastomotic urethroplasty). We only recently started using standardized questionnaires to measure erectile function so this metric was not included in this analysis. Patient comorbidity data were simply noted as "presence or absence," and therefore severity or history of "resolved disease" data was not included.

## CONCLUSIONS

A paucity of literature exists evaluating the success of urethroplasty for radiation-induced urethral stricture disease. This study's urethroplasty success rate was 90%. These excellent results are consistent with other research in suggesting urethroplasty is appropriate and feasible in the setting of prior radiation therapy. Reports in the literature consistently demonstrate higher rates of bulbomembranous stricture disease, with the majority treated by excision and primary anastomosis.

### References


1. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med*. 1997;337:295-300.
2. Leibovich BC, Engen DE, Patterson DE, et al. Benefit of adjuvant radiation therapy for localized prostate cancer with a positive surgical margin. *J Urol*. 2000;163:1178-1182.
3. Ragde H, Grado GL, Nadir BS. Brachytherapy for clinically localized prostate cancer: thirteen-year disease-free survival of 769 consecutive prostate cancer patients treated with permanent implants alone. *Arch Esp Urol*. 2001;54:739-747.
4. Catalona WJ, Han M. Definitive therapy for localized prostate cancer—an overview. In: Wein AJ, ed. *Campbell-Walsh Urology*, Vol. 3. Philadelphia: Saunders; 2011.
5. Yeoh EE, Botten R, Russo A, et al. Chronic effects of therapeutic irradiation for localized prostatic carcinoma on anorectal function. *Int J Radiat Oncol Biol Phys*. 2000;47:915-924.
6. Miller K, Poch M, Brandes SB. Urethral stricture and urethroplasty in the pelvic irradiated patient. In: Brandes MD, ed. *Current Clinical Urology: Urethral Reconstructive Surgery*, Vol. 241. Totowa: Humana Press; 2008:241-249.
7. Elliott SP, Meng MV, Elkin EP, et al. Incidence of urethral stricture after primary treatment for prostate cancer: data from CaPSURE. *J Urol*. 2007;178:529-534.
8. Mohammed N, Kestin L, Ghilezan M, et al. Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82(1):204-212.
9. Sullivan L, Williams SG, Tai KH, et al. Urethral stricture following high dose rate brachytherapy for prostate cancer. *Radiother Oncol*. 2009;91:232-236.
10. Rourke KF, Jordan GH. Primary urethral reconstruction: the cost minimized approach to the bulbous urethral stricture. *J Urol*. 2005; 173:1206-1210.
11. Whitson JM, McAninch JW, Elliott SP, et al. Long-term efficacy of distal penile circular fasciocutaneous flaps for single stage reconstruction of complex anterior urethral stricture disease. *J Urol*. 2008;179:2259-2264.
12. Fichtner J, Filipas D, Fisch M, et al. Long-term outcome of ventral buccal mucosa onlay graft urethroplasty for urethral stricture repair. *Urology* 2004;64:648-650.
13. Barbagli G, Morgia G, Lazzeri M. Retrospective outcome analysis of one-stage penile urethroplasty using a flap or graft in a homogeneous series of patients. *BJU Int*. 2008;102:853-860.
14. Meeks JJ, Brandes SB, Morey AF, et al. Urethroplasty for radiotherapy induced bulbomembranous strictures: multi-institutional experience. *J Urol*. 2011;185:1761-1765.
15. Elliott SP, McAninch JW, Chi T, et al. Management of severe urethral complications of prostate cancer therapy. *J Urol*. 2006;176: 2508-2513.
16. Heyns CF, Marais DC. Prospective evaluation of the American Urological Association symptom index and peak urinary flow rate for the followup of men with known urethral stricture disease. *J Urol*. 2002;168:2051-2054.
17. Breyer BN, McAninch JW, Whitson JM, et al. Multivariate analysis of risk factors for long-term urethroplasty outcome. *J Urol*. 2010;183:613-617.
18. Marks LB, Carroll PR, Dugan TC, et al. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys*. 1995;31:1257-1280.
19. Culty T, Boccon-Gibod L. Anastomotic urethroplasty for posttraumatic urethral stricture: previous urethral manipulation has a negative impact on the final outcome. *J Urol*. 2007;177:1374-1377.
20. Martínez-Piñeiro JA, Cárcamo P, García Matres MJ, et al. Excision and anastomotic repair for urethral stricture disease: experience with 150 cases. *Eur Urol*. 1997;32:433-441.


## EDITORIAL COMMENT

The authors describe a large (29 patients) single-surgeon series of urethroplasty for radiation induced urethral strictures. With more prostate cancers detected every year, the rate of radiation-induced strictures will increase over time. First, the authors should be congratulated for achieving a high rate of success (90%). This rate is comparable with a previous multi-institutional series that reported a success rate >80% with reconstruction.[1] There is now evidence that it is possible to reconstruct these very challenging surgical patients. With strictures occurring at an incidence of at least 2% of patients who receive radiotherapy,[2] there must be more than the 59 patients treated in these series who are candidates for surgical reconstruction. As more urologists are trained in surgical reconstruction, more of these cases may be attempted with excellent outcomes. Second, the authors describe their surgical outcomes but do not address important quality-of-life outcomes, including patient satisfaction and erectile function. In a prior series, erectile dysfunction and incontinence rates approached 50% after reconstruction.

Although these men seem more satisfied without suprapubic tubes after reconstruction, an important result will include patient-reported outcomes. It is hoped that prospective quality-of-life studies will help confirm that these surgical efforts result in satisfied patients.

**Joshua J. Meeks, M.D.,** Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

## References

1. Meeks JJ, Brandes SB, Morey AF, et al. Urethroplasty for radiotherapy induced bulbomembranous strictures: a multi-institutional experience. *J Urol.* 2011;185:1761-1765.
2. Elliott SP, Meng MV, Elkin EP, et al. Incidence of urethral stricture after primary treatment for prostate cancer: data From CaPSURE. *J Urol.* 2007;178:529-534; discussion 534.

doi:10.1016/j.urology.2011.11.081
UROLOGY 79: 1405–1406, 2012. 