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Urinary Diversion for Severe Urinary Adverse Events of Prostate Radiation: Results from a Multi-Institutional Study

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Purpose: To evaluate the short and long-term surgical outcomes after urinary diversion (UD) done for urinary adverse events (UAEs) arising from prostate radiation therapy (RT). We hypothesized patient characteristics are associated with complications after UD.

Materials and Methods: A retrospective cohort study of 100 men who underwent UD (urinary conduit or continent catheterizable pouch) due to UAEs following prostate RT from 2007-2016 from nine academic centers in the United States. Outcome measurements included predictors of short and long-term complications, and readmission after UD in post-RT prostate cancer patients. The data was summarized using descriptive statistics and univariate associations with complications were identified with logistic regression controlling for center.

Results: Mean age was 71 years and median time from RT to UD was 8 years. Eighty-one (81%) patients had combined-modality therapy (radical prostatectomy plus RT or various combinations of RT). Grade 3a or greater Clavien-Dindo complications occurred in 31 (35%) men including 4 deaths (4.5%). Normal weight men had higher short-term complications compared to overweight (odds ratio (OR)= 4.9, 95% CI: 1.3-23.1, p=0.02) and obese men (OR=6.3, 95% CI: 1.6-31.1, p=0.009). Readmission within 6 weeks of surgery occurred in 35 (38%) men. Surgery was needed to treat long-term post UD complications in 19 (22%) patients with a median follow-up of 16.3 months.

Conclusions: UD after prostate RT has a considerable short and long-term surgical complication rate. Urinary diversion most often cannot be avoided in these patients, but appreciation of the risks allows for informed shared decision making between surgeons and patients.

Key words: urinary diversion, radiation, prostate cancer, complications
Word count: Abstract – 250, Manuscript - 2497

There are estimated to be close to 3 million U.S. men diagnosed with prostate cancer[1]. Radiation therapy (RT) is used to treat up to 37% of men within 6 months of diagnosis of prostate cancer[2], and many men receive RT later during the course of their disease; this translates to approximately 1 million prostate cancer survivors who have received RT.

The true incidence of long-term urinary adverse events (UAEs) for RT for prostate cancer treatment is not known, but in most studies high-grade UAEs are rare. Previous studies of the surgical management of post RT UAEs often focus on the subsets of patients, such as those with recto-urethral fistula[3] or bony complications in the pelvis[4,5]. Some UAEs after RT, however, are so severe that primary repair is not feasible and patients must undergo urinary diversion (UD) often combined with cystectomy. Men undergoing UD after RT for prostate cancer have not been well studied and little is known about their short or long-term complications after this surgery. The patient demographic and clinical characteristics, as well as the surgical approach differ from patients undergoing radical cystectomy for bladder cancer; so, the outcomes may not be readily comparable between these patients.

Our aim was to establish the morbidity and mortality of UD in patients who have severe UAEs after prostate RT. We hypothesized that pre-operative patient characteristics might predict both short and long-term complications after UD.

MATERIALS AND METHODS:

After institutional review board approval, 9 sites in the Trauma and Urologic Reconstruction Network of Surgeons (TURNSresearch.org) and the Neurogenic Bladder Research Group (NBRG.org) retrospectively reviewed and contributed data. The study period was from 2007-2016, which represented 50 'center years' (defined as the time a surgeon was at a contributing center). Exclusion criteria included: pelvic malignancy other than prostate cancer and cystectomy for bladder cancer after a history of RT for prostate cancer.

Variables

Pre-operative data included: age, body mass index (BMI), which was treated as both categorical variable (normal weight (BMI <25 kg/m^2), overweight (BMI 25- 29.9 kg/m^2), obese (BMI ≥ 30 kg/m^2)) and as a continuous variable, comorbidities quantified with the Charlson comorbidity index[6] divided into tertiles, type of RT, presenting urologic problems (intractable incontinence, urethral stricture / bladder neck contracture, fistula or perforation of urinary tract (rectal, cutaneous, soft tissue, and bony pelvis), urinary infection / abscess, hemorrhagic cystitis, and tissue necrosis (prostate, bladder) - men could have more than one problem on presentation, number of surgical interventions for UAEs prior to UD, and latency period between RT and UD. Operative information included: type of UD, length of stay, and ancillary surgical procedures at the time of UD. Men were grouped by location UAEs, which included: bladder, outlet / urethra, or both

bladder and outlet / urethra. Post-operative data included readmission rates within 6 weeks of UD, modified Clavien-Dindo (Clavien) grading[7] of major short-term (< 90 day) post-operative complications (Grade 3a-5), and long-term (>90 day) complications requiring surgical intervention (Grade 3b). Patients were classified for short-term complications by their highest Clavien complication grade.

Statistical Analysis

Clinical characteristics were summarized as n (%) for categorical variables and mean (± standard deviation, SD) or median (interquartile range, IQR) for continuous variables. Firth's penalized logistic regression was used to test for associations between the outcomes: 1) short-term post-operative complications and 2) readmission within 6 weeks; with each demographic, pre-operative, and post-operative variable (tested separately) controlling for the nine centers. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported from these models. An extension of Firth's methodology to Cox regression was used for analysis of long-term complications, and hazards ratios (HRs) and 95% CIs were reported. The cohorts for analysis included: 1) short-term complications - patients who died or had a minimum of 3 months follow-up 2) readmission - patients who died or had a minimum of 6 weeks of follow-up 3) long-term complications - patients who survived and had greater than 3 months of follow-up. A Kaplan-Meier plot was used to illustrate the cumulative long-term surgical complications (patients were censored after their first surgical complication). Statistical significance was assessed at a 0.05 level, and all tests were two-tailed. Analyses were conducted in R v. 3.03 software using the logistf and coxphf packages[7].

RESULTS:

Demographics

A total of 105 men were identified undergoing UD with a history of RT for prostate cancer. Four men were excluded due to concomitant pelvic cancer other than prostate cancer, and one because he had augmentation cystoplasty. The 100 men meeting the inclusion criteria had a mean age of 71.0 ± 7.9 years (range: 51-89). The median time from RT treatment to UD was 8 (interquartile range (IQR): 5-12, range: 0.8-31) years. The mean estimated number of operations for RT-associated UAEs prior to UD was 3.7 ± 2.2 operations (range: 0-15). The Charlson comorbidity index divided in tertiles included 49 men (49%) between 2-5, 22 men (22%) 6, and 28 men (28%) ≥ 7. Men were normal weight in 22%, overweight in 42%, and obese in 36% (Table 1).

Previous Radiation Therapy

Radiation therapy for prostate cancer included 19 (19%) patients that were treated with single-modality therapy with RT alone and 81 (81%) patients who underwent combined-modality therapy (Table 1). The most common combined modality therapy was RP + EBRT n = 51 (51%). Prostate cryoablation was used in 10 men (2 men who had single-modality RT prior to cyrotherapy and 8 (8%) men who had combined-modality RT prior to cryotherapy).

Radiation Related Urinary Adverse Events

RT UAEs leading to UD included: intractable incontinence (55%), urethral stricture / bladder neck contracture (52%), fistula or perforation (42%), urinary infection / abscess (32%), hemorrhagic cystitis (25%), and necrosis of the bladder or urethra / prostate (25%). The urethra / outlet was the location of UAEs in 48 (48%), the bladder in 7 (7%), and both urethra / outlet and bladder in 45 (45%) men.

Urinary Diversions

Sixteen (16%) patients underwent continent catheterizable pouch and 84 (84%) patients underwent urinary conduit (ileal conduit n = 78 (93%), colon conduit n = 6 (7%)). Eighty-three (83%) patients underwent cystectomy at the time of urinary diversion (Table 1). Other procedures at the time of UD included prostatectomy (12), bowel resection (6), fistula excision (3), artificial urinary sphincter explantation (3), gracilis flap (1), drainage of abscess (1), pubic symphysis debridement (1), and penile prosthesis explantation (1).

Short-term Complications and Readmission

There were 89 patients that had follow up > 90 days or who died in the peri-operative period. Clavien Grade ≥ 3a complications occurred within 90 days following UD in 31 (36%) men (Table 2), including Grade 3a (intervention without general anesthesia) in 3 (3%), Grade 3b (reoperation) in 11 (12%), Grade 4 (ICU re-admission for complications) in 13 (15%), and Grade 5 (death) in 4 (4.5%). Deaths included: exacerbation of end-stage liver failure from a history of choleangiocarcinoma, post-operative hemorrhage, rectal perforation, and septic shock. Thirteen (15%) of men underwent early reoperation (11 classified as grade 3b and 2 additional men that had higher grade complications but also required operative intervention). These 13 men underwent 16 total operations within 90 days of surgery (Table 2). The odds of a major short–term complication (Clavien ≥ 3a) was 4.9 (CI: 1.3-23.1, p=0.02) and 6.3 (CI: 1.6-31.1, p=0.009) times higher in normal weight men, compared to overweight or obese men respectively. When BMI was treated as a continuous variable there was a 9% risk reduction of short-term complication for every 1-point increase in BMI (OR=0.91, 95% CI: 0.83-0.99, p=0.031). There were no associations between short-term UD complications and age, type of RT, timing of RT, location of UAE, Charlson comorbidity index tertiles, prior number of urologic procedures, concomitant additional major surgeries, or type of UD (Table 3).

Hospital stay was longer after UD in men with short-term Clavien Grade ≥ 3a complications versus those without a complication (mean 10 days versus 15.2 days, p=0.002).

There were 93 men with 6 weeks of follow up or more and 35 (38%) were readmitted to the hospital for post-operative complications. Using the same variables as short-term complications, the only association with a higher risk of readmission was lower BMI when BMI was analyzed as a continuous variable. The rate of readmission was decreased by 11% for every 1-point increase in BMI (OR=0.89, 95% CI: 0.80-0.97, p=0.009).

Long-term Complications

15 men were excluded from the analysis of long-term complications due to death (n=4) or lost to follow-up (n=11) within 90 days. The median follow-up was 16.3 (IQR: 9.5-35.1, range 3.1-96.9) months for the 85 men in the long-term complications analysis. 19/85 (22%) men underwent a total of 27 surgeries for long-term complications; the Kaplan-Meier plot of the cumulative incidence of reoperation for long-term complications is pictured in Figure 1. Reoperations are summarized in Table 2. There was no association between long-term complications and the same parameters we analyzed for short-term complications.

DISCUSSION:

We found a high rate of complications associated with UD performed for severe UAEs of prostate RT. These included: death (<90 days) in 4.5%, reoperation (<90 days) in 15%,

Clavien ≥ 3 complications (<90 days) in 36%, and readmission (<6 weeks) in 38%. In addition, we found a high long-term surgical burden with 15% of men needing additional surgery in the first year after UD. However, the UDs were performed in a high-risk group of men who had failed all other options short of UD for management of their severe UAEs after RT. Prior to operation, men often suffered from chronic infection, necrosis of the urinary tract, and urinary fistula, likely leading to a state of malnutrition. In addition, half of the men presented with a Charlson comorbidity score >5, illustrating that their overall health was poor too. The only association with poor outcomes in our analysis was lower BMI, which may support nutrition as an important factor.

In the one study to date examining UD after prostate RT, Faris et al (2014) focused on the presentation and symptom progression leading to UD[8]. In this single institution study, 30 men underwent an average of 4.4 urologic surgeries attempting to treat RT UAEs prior to UD, which was very similar to our study (3.7 operations prior to UD). This study did not discuss post-operative outcomes, but the UAEs, which led to UD were similar to our patients (fistula, irreparable stricture / outlet pathology, and radiation cystitis).

We found a higher rate of major short-term complications in normal weight compared to overweight and obese men. This might have been observed because normal weight men, in this age group, might not necessarily be healthier but instead have normal weight due to malnutrition resulting from their chronic disease state. An alternative explanation is the 'obesity paradox': where extra weight is counterintuitively protective and associated with greater survival during physiologic stress, which has been demonstrated in two recent meta-analyses of patients in the intensive care setting[9,10].

A high proportion of men (81%) who underwent UD in our study had combined-modality therapy, the most frequent being RP and subsequent RT (51% of the entire study population). Some studies have reported that RT after RP has minimal long-term urinary consequences.[11] In contrast, other studies have reported a higher morbidity of subsequent RT after RP. The EORTC trial 22911 showed 11% more UAEs (any grade) at 10 years follow-up, in men with RP + RT, compared to RP alone[12]. In addition, Surveillance Epidemiology and End Results (SEER)-Medicare data estimated the 10-year incidence of grade 3-4 UAEs to be 9.2% higher in the RP + RT patients than those receiving only RP[13]. We are unable to determine the incidence of UAEs in patients undergoing combined-modality treatment for prostate cancer, however, the high rate of combined-modality therapy (81%) in men needing UD intuitively points to its increased toxicity.

In our study, the high-grade complication rate and mortality risk with UD was higher than that reported in contemporary series of radical cystectomy and UD for bladder cancer[14-16]. Schiavina et al (2013) showed a major complication rate of 17.3% and a 90-day mortality of 4.5%[16]. Similarly, Shabsigh et al (2009) demonstrated a major complication (Clavien grade 3-5) rate of 13% and a 90-day mortality of 2% in 1142 bladder cancer patients. Significant predictors of major complications, in these studies, included: the American Society of Anesthesiologists (ASA) score, age at time of surgery, prior abdominal surgery, and estimated blood loss during surgery[1516]. In contrast to our patients, only 30% of subjects had a Charlson comorbidity index score of ≥2 compared to 100% of men in our study (50% Charlson comorbidity index ≥ 5) - an observation that may explain why we found a higher rate of major complications (36%) and a comparable or higher perioperative mortality (4.5%) than these studies. When comparing our

outcomes to other series of post RT UD, they were very similar. Eisenberg et al (2010) reported, in a post-RT UD series of 148 patients, with a 32.4% major complications and a 90-day mortality of 6.1%, which was almost identical to our results[17].

Our long-term complication rate requiring reoperation was 20% at a median follow-up of 16.3 months and was not associated with a specific type of UD or any other patient characteristics. Other studies have shown a high rate of long-term complications especially among radiated patients undergoing continent catheterizable diversions. One of the highest rates was in cervical cancer patients who had RT and underwent UD with an Indiana pouch where 67% required a second operation at a mean follow up time of 48.5 months[18]. There is no doubt our long-term complications will rise as our follow-up time increases.

Some major limitations of our study are the retrospective design and referral bias, which did not allow us to determine the rate of UAEs of RT in our communities, as well as how many men experienced severe UAEs but never sought UD. Another weakness of the study is lack of longer-term follow-up to estimate the long-term risk of additional surgeries related to UD. We included this data, even though it is limited by a median follow up of 16.5 months, because it illustrates that even in this short time frame many men require additional surgery. Our study was underpowered to detect a difference between types of UD and complications due to the predominance of conduits, as well as differences in outcomes between centers. Lower BMI was associated with a higher complication rate, maybe due to relative malnutrition, but better surrogates for preoperative nutrition status such as albumin, prealbumin, and transferrin were not available in our retrospective review.

CONCLUSIONS:

Urinary diversion in men after prostate RT has considerable short and long-term morbidity. Most men that need UD have undergone combined-modality treatment with a long latency period between RT and UD. Normal weight men have a higher short-term complication rate compared to overweight and obese men. Urinary diversion is a treatment of last resort in the majority of these men and cannot be avoided in most cases, however, understanding the true morbidity and mortality associated with this treatment allows for informed shared decisions between patients and surgeons.

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Table 1. Patient demographics and clinical characteristics in 100 patietns with severe urinary adverse events after radiotherapy for prostate cancer

	Variable		Range
Age at UD	Mean (SD)	71 (7.9)	51-89
BMI (kg/m^2**)**	<25	22 (22%)	
	25-29.9	42 (42%)	
	>30	36 (36%)	
RT Type			
Combined modality therapy		**81 (81%)**	
	RP + EBRT	49 (49%)	
	BT + EBRT	17 (17%)	
	HDR + Boost	12 (12%)	
	Other combinations*	2 (2%)	
Single modality therapy		**19 (19%)**	
	EBRT	12 (12%)	
	HDR	2 (2%)	
	BT	4 (4%)	
	Proton Beam	1 (1%)	
RT UAE	Intractable incontinence	55 (55%)	
	Urethral Stricture/Bladder Neck Contracture	52 (52%)	
	Fistula / perforation	42 (42%)	
	Infection/abscess	32 (32%)	
	Hemorrhagic cystitis	26 (26%)	
	Necrosis	25 (25%)	
Primary location of UAE	Urethra / outlet	48 (48%)	
	Bladder	7 (7%)	
	Urethra / outlet + bladder	45 (45%)	
Operative interventions prior to UD	Mean (SD)	3.7 (2.2)	0-15
Time from RT to UD (years)	Median (IQR)	8 (5, 12)	0.8-31
	Range	(0.8, 31)	
Urinary diversion type	Continent Catheterizable Pouch	16 (16%)	
	Conduit	84 (84%)	
Cystectomy	Cystectomy	83 (83%)	
Charleson comorbidity index	2-5	49 (49%)	
	6	22 (22%)	
	≥7	28 (28%)	
Length of stay	Mean (SD)	11.9 (10)	

*51 total men had RP and RT (49 with EBRT and 2 with RP and XX and XX)
(UD) urinary diversion, (SD) standard deviation, (BMI) body mass index, (RT) radiotherapy, (UAE) urinary adverse event, (RP) radical prostatectomy, (EBRT) external beam radiotherapy, (BT) low-dose rate brachytherapy, (HDR) high-dose rate brachytherapy, (IQR) intraquartile range

Table 2: Summary of overall complications. Short-term complications (less than 90 days) in 89 paitents who died (n=4) or had follow-up > 90 days (n=85). Long-term complications (greater than 90 days) in 85 men with > 90 days of follow up and survived (n=85). Readmission rate in 94 men with > 6 weeks of follow-up.

	Variable	**N**
High-grade Clavien short-term complications < 90 days	**3a-5**	**31 (36%)**
	3a	3 (3%)
	3b	11 (12%)
	4	13 (15%)
	5	4 (4.5%)
Short-term surgical complications < 90 days	**Total**	**13 (16 operations in 13 men)**
	Repair of urine leak	4
	Lysis of adhesions	2
	I&D surgical site infection	2
	Drainage of pelvic abscess	2
	Exploration for hemorrhage	1
	Debridement of osteomyelitis	1
	Retained foriegh body	1
	Recto-urethral fistula repair	1
	Excision of hernia mesh	1
	Ureteroscopy to remove stents	1
Long-term surgical complications > 90 days	**Total**	**27 (32%)**
	Ureteral stenosis	10
	Parastomal hernia	7
	Catheterizable channel stenosis	3
	Chronic pelvic infection	2
	Ventral hernia	1
	Conduit stenosis	1
	Bowel obstruction	1
	Non-healing wound	1
	Chronic testicular pain	1
Readmission < 6 weeks		36 (38%)
Follow-up time after UD	Median, range (months)	16.5, 3-98

(UD) urinary diversion, (I&D) incision and drainage

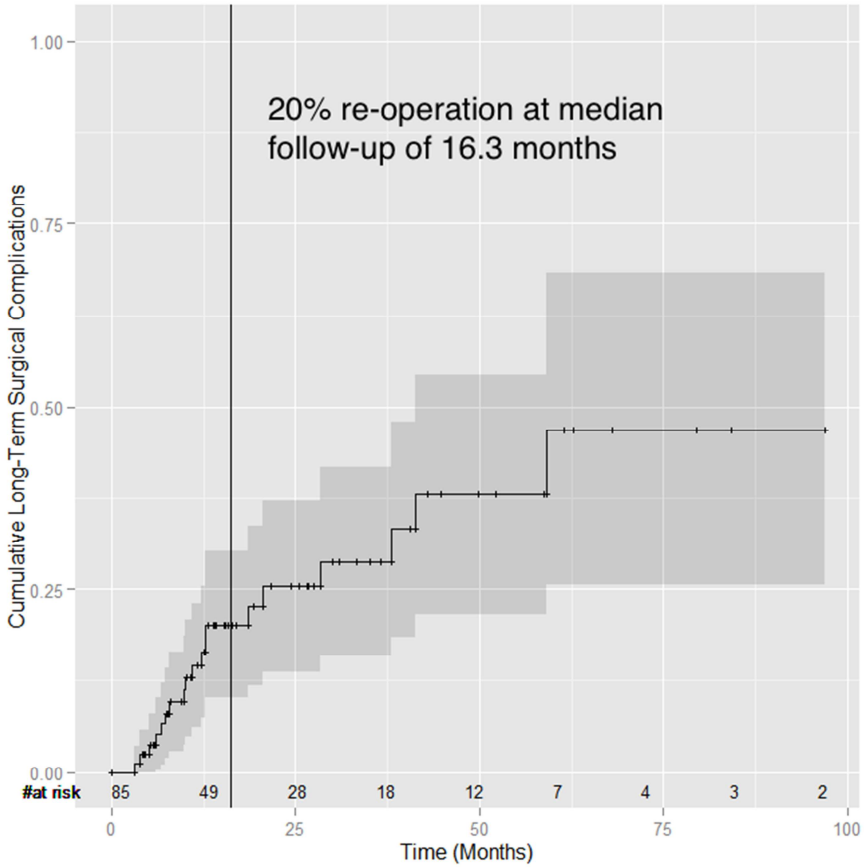
Table 3: Associations with short-term complications (< 90 days) in 89 men who either died (n=4) or had > 90 days of follow-up (n=85).

Short-term Clavien complications (<90 days)					
Variable		**No Clavien grade 3a-5 (n=58)**	**Clavien grade 3a-5 (n=31)**	**OR (95%CI)**	**P-value**
Age at UD	Mean (SD)	70.9 (7.4)	70.7 (8)	0.99(0.93~1.05)	0.63
BMI (kg/m^2)‡	<25	9 (47%)	10 (53%)	Reference	-
	25-29.9	25 (69%)	11 (31%)	0.2(0.04~0.79)	0.02*
	>30	23 (72%)	9 (28%)	0.16(0.03~0.64)	0.009*
Primary location of UAE					
Urethra / outlet		24 (41%)	17 (55%)	Reference	
Bladder		5 (9%)	1 (3%)	0.87(0.06~12.26)	0.91
Urethra / outlet + bladder		29 (50%)	13 (42%)	0.5(0.17~1.41)	0.19
Operative interventions prior to UD	Mean (SD)	3.9 (2.6)	3.7 (1.5)	1.11(0.84~1.49)	0.45
Type of UD					
Conduit		49 (67%)	24 (33%)	Reference	-
Continent catheterizable pouc		9 (56%)	7 (44%)	0.93(0.29~2.91)	0.9
Concomitant procedures		46 (65%)	25 (35%)	0.58(0.15~2.12)	0.4
Charleson comorbidity index	2-5	27 (60%)	18 (40%)	Reference	-
	6	15 (26%)	5 (16%)	0.6(0.17~1.9)	0.39
	≥7	15 (26%)	8 (26%)	0.86(0.24~2.96)	0.82
Time from RT to UD (years	Mean (SD)	8.7 (5.3)	8.3 (4.3)	0.99(0.9~1.08)	0.78
Combined-modality therap		45 (63%)	26 (37%)	1.83(0.59~6.24)	0.3
Length of stay	Mean (SD)	10 (9.9)	15.2 (10.1)	1.14(1.04~1.3)	0.002*

(OR) odds ratio, (UD) urinary diversion, (SD) standard deviation, (BMI) body mass index, (UAE) urinary adverse event, (RT) radiotherapy.

‡ Associations of BMI data are expressed as reduced risk in overweight and obese men compared to normal weight men, in the text these are expressed as an increased risk of complicaitons in normal weight men compared to overweight and obese men.

Figure 1: Kaplan-Meier plot of cumulative long-term surgical complications. The black line indicates the 16.3 months median follow up, where the long-term risk of surgical interventions was 20% (patients were censored after their first surgical complication).



At 6 months, the cumulative operative LTC rate is 3.8% (95% CI: 0-7.9%), and there were 70 patients with data that were included in this estimate. At 1 year, the cumulative operative LTC rate was 14.6% (95% CI: 5.7-22.7%), where there were 55 patients with available data at this time point.

(UD) urinary diversion, (RT) radiotherapy, (UAE) urinary adverse event, (RP) radical prostatectomy, (EBRT) external beam radiotherapy, (BT) low-dose rate brachytherapy, (HDR) high-dose rate brachytherapy, (IQR) intraquartile range, (OR) odds ratio, (SD) standard deviation, (BMI) body mass index