Inflatable penile prosthesis outcomes after pelvic radiation

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Introduction: *Few studies have compared surgical outcomes after 3-piece inflatable penile prosthesis (IPP) surgery in patients exposed to pelvic radiation therapy (RT) compared to a radiation naïve control group.*

Materials and methods: *A total of 715 consecutive patients underwent 3-piece IPP placement between 2007-2018. There were 101 men exposed to pelvic RT before or after IPP for a variety of malignancies and 153 men met inclusion criteria for the control group, which included men undergoing IPP surgery with a history of radical prostatectomy but no exposure to pelvic RT.*

Results: *Patients in the RT group had a higher body mass index (kg/m^2) (28.7 versus 27.8, p = 0.003) and higher Charlson co-morbidity index score (6 versus 5; p < 0.001). At a median follow up of 5 years (IQR 2-8 years), there was an 18.4% surgical complication rate in the radiation group compared to 11.5% in the control group, though this was not statistically significant (p = 0.141). Timing of radiation, prior artificial urinary sphincter (AUS) status, co-implantation of an AUS, and brand of prosthesis were not associated with increased rate of complications. On multivariable logistic regression analysis, exposure to RT was not significantly associated with increased risks of complications (OR: 1.31; CI 0.55-3.12).*

Conclusions: *This study shows no significant increase in risk of surgical complication in patients exposed to pelvic RT and supports the use of IPP in men with a history of RT and refractory erectile dysfunction.*

Key Words: implantations, penile prosthesis, injury, radiation, erectile dysfunction

Introduction

Erectile dysfunction (ED) is a common side effect of pelvic radiation therapy (RT) with estimated prevalence rates of 22%-84%.[1] This can be detrimental to patient quality of life.[2] The exact mechanism for RT induced ED is not understood, however, studies have shown that RT causes pathologic tissue changes. This includes ionizing injury to vascular endothelial cells causing corporeal fibrosis as well as damage to periprostatic neurovascular bundles, both of which can contribute to ED.[3]

ED management in the post RT patient is similar to that of patients with a history of radical prostatectomy or other organic etiology and generally progresses from non-surgical toward surgical options. The 3-piece inflatable penile prosthesis (IPP) is a well-accepted treatment option for patients with refractory ED, however, urologists may be reluctant to offer this treatment to patients with a history of RT due to perception of increased risk of complications in this patient population. Radiation induced fibrotic changes may increase the risk of intraoperative complications such as corporeal or urethral injury, injury to adjacent organs during reservoir placement or late complications such as infection, erosion, or device malfunction. This has been demonstrated in limited small clinical studies and case reports.[4-6] However, there is conflicting literature as to whether exposure to RT poses an increased risk of adverse outcome after surgery. A large Medicare database was queried and concluded no difference in re-operation rates between radiation and radiation naïve patients.[7] Another single center study examined a cohort of IPP patients exposed to radiation and concluded no increased risk of complication compared to published

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rates in a non-radiated population.[8] Acknowledged limitations of these studies included lack of a control group, limited analysis of type and dose of radiation, as well as omission in reporting comorbid risk factors.

Our goal was to define the risk of pelvic radiation exposure on IPP surgical outcomes. In this study, we retrospectively examined surgical outcomes after IPP implantation in patients exposed to pelvic RT compared to a radiation naïve control group.

Materials and methods

A retrospective database of 715 consecutive patients undergoing IPP implantation at a single tertiary care academic institution from 2007 (commencement of electronic medical records) to 2018 was queried. Two different models of 3-piece IPPs were used in this study: AMS 700 (Boston Scientific, Marlborough, MA, USA) and Coloplast Titan (Coloplast, Humlebaek, Denmark). The RT cohort included men who underwent placement of a 3-piece IPP for erectile dysfunction secondary to prostatectomy or RT. All patients underwent external beam RT, brachytherapy, or both. Radiation was administered prior to or after insertion of the prosthesis. The control group included all men who had previously undergone prostatectomy but reported no history of receiving RT. Men were excluded if data were incomplete in the electronic medical records or if men did not follow up after IPP implantation. All men underwent placement of IPP after failure of conservative ED therapies.

Patient follow up was generally scheduled for 4-6 weeks and 3 months following surgery, and as needed thereafter. To obtain long term follow up, patients were contacted in late 2018 and asked about the IPP functionality and satisfaction with their device. If patients had any issues with their prosthesis, they were invited to follow up in clinic.

Patient demographics including age, body mass index (BMI), oncologic diagnosis, Charlson Comorbidity Index (CCI), year of prostatectomy, year of RT, type of RT, cumulative RT dose, whether RT was given prior to or following prosthesis placement, type of IPP placed, co-placement of artificial urinary sphincter (AUS), and follow up duration were recorded. The primary endpoint was any complication from IPP implantation, which included infection, erosion, migration, and device malfunction.

Continuous outcomes were compared with Wilcoxon rank sum tests and categorical variables with chi-square tests. Multivariable logistic regression models were constructed to evaluate the association of RT and other variables with complications following IPP placement. Cox proportional hazards regression models assessed associations with revision surgery events over time. Institutional review board approval was obtained prior to the development of a penile prosthesis database. All statistical analyses were executed using STATA v.15.0 (StataCorp LP, College Station, TX, USA). P values of < 0.05 were considered statistically significant.

Results

A total of 101 men met inclusion criteria for the RT cohort with a median age of 65 years (IQR: 60-71). Ninety men underwent RT prior to surgery, and 11 underwent RT after surgery, Table 1. There were 153 men included in the control group with a median age of 65 years (IQR: 60-71). The groups undergoing RT prior to and after surgery were otherwise comparable in age, BMI, and CCI. While prostate cancer was the most common oncologic diagnosis in the RT cohort encompassing 92.1% of men, 8 men had non-prostate cancer indications for radiation: 4 for rectal cancer, 2 for lymphoma, and 2 for pelvic sarcoma. External beam radiation was the most common type of RT (61.4%) followed by brachytherapy (14.9%), and only 2 men (2%) underwent both external beam radiation and brachytherapy. A total of 52 men underwent both RT and radical prostatectomy while 49 men underwent only RT. When comparing the RT to the control group, age was comparable, as is seen in Table 2, but men receiving RT had a greater BMI (kg/m^2) (28.7 versus 27.8, $p = 0.003$) and had a higher Charlson co-morbidity index score (6 versus 5, $p < 0.001$).

At a median follow up of 5 years (IQR 2-8 years), the RT group had more IPP surgical complications (18.4% versus 11.5%) when compared with controls. However, this difference was not statistically significant overall ($p = 0.141$), nor were there statistically significant differences for any specific type of complication, Table 3. Timing of radiation, prior AUS status, co-implantation of an AUS, and brand of prosthesis were not associated with increased rate of complications.

On multivariable logistic regression analysis, Table 4, controlling for age, CCI, BMI, prior AUS implant, dual implantation of AUS along with IPP, and year of IPP implant, exposure to RT was not significantly associated with increased rates of complications (Model 1 – OR: 1.31; CI 0.55-3.12). Year of IPP implant was no longer significant when controlling for potential confounders. In a subset analysis assessing type of radiation and dose of radiation, neither was found to be associated with a higher rate of complications.

Finally, we assessed device survival via Kaplan Meier survival curves comparing both study populations, Figure 1. Overall, there were no significant differences between the two groups (log-rank test $p = 0.418$) and

		Any RT (N=101) Median/N	IQR/(%)	RT before IPP (N=90) Median/N	IQR/(%)	RT after IPP (N=11) Median/N	IQR/(%)	p-value
Age		65	60-71	66	60-71	62	59-66	0.354
BMI		28.7	25.7-32.9	28.5	25.6-32.9	29	26-35.3	0.717
CCI		6	5-6	6	4-6	5	5-7	0.725
Oncologic Diagnosi	***Prostate Cancer***	93	(92.1)	82	(91.1)	11	(100.0)	0.786
	Other	8	(7.9)	8	(8.9)	0	-	
Treatment	***RP and RT (before IPP)***	41	(40.6)	41	(45.6)	0	-	N/A
	RT (Prostate Cancer)	41	(40.6)	41	(45.6)	0	-	
	RT (Not Prostate Cancer	8	(7.9)	8	(8.9)	0	-	
	RT after IPP	11	(10.9)	0	-	11	(100.0)	
RT Type	***EBRT***	62	(61.4)	52	(57.8)	10	(90.9)	0.192
	Brachytherapy	15	(14.9)	15	(16.7)	0	-	
	EBRT + Brachytherapy	2	(2.0)	2	(2.2)	0	-	
	Unknown	22	(21.8)	21	(23.3)	1	(9.1)	
RT Dose (rads)		7020	6660-7800	7020	6660-7800	6210	4063-7380	0.354
RP Year		2008	2002-2009	2008	2002-2009	N/A	N/A	N/A
RT Year		2008	2004-2011	2008	2004-2010	2015	2007-2017	0.192
IPP Year		2011	2009-2014	2011	2009-2014	2011	2003-2013	0.014
IPP Type	***AMS***	81	(80.2)	72	(80.0)	9	(81.8)	0.045
	Coloplast	15	(14.9)	15	(16.7)	0	-	
	Unknown	5	(5.0)	3	(3.3)	2	(18.2)	
Prior AUS		11	(10.9)	8	(8.9)	3	(27.3)	0.065
Prior Other Incontinence Procedure		5	(5.0)	5	(5.6)	0	-	0.423
Dual Implant		17	(16.8)	17	(18.9)	0	-	0.114

RT = radiation therapy; BMI = body mass index; CCI = Charlson Comorbidity Index; RP = radical prostatectomy; IPP = inflatable penile prosthesis; EBRT = external bean radiation therapy; AMS = Ameircan Medical System; AUS = artificial urinary sphincter

Table 1. Comparison of baseline characteristics based on timing of radiation therapy.

		Entire Cohort (N=253) Median/N	IQR/(%)	Control (N=152) Median/N	IQR/(%)	Any RT (N=101) Median/N	IQR/(%)	p-value
Age		65	60-71	65	60-71	65	60-71	0.959
BMI		28.1	25.8-31.1	27.8	25.8-29.9	28.7	25.7-32.9	0.003
CCI		5	4-6	5	4-6	6	5-6	0.000
Oncologic Diagnos	***Prostate Cancer***	245	(96.8)	152	(100.0)	93	(92.1)	0.006
	Other	8	(3.2)	0	-	8	(7.9)	
Treatment	***RP and RT (before IPP)***	41	(16.2)	0	-	41	(40.6)	N/A
	RP Alone	152	(60.1)	152	(100.0)	0	-	
	RT (Prostate Cancer)	41	(16.2)	0	-	41	(40.6)	
	RT (Not Prostate Cancer)	8	(3.2)	0	-	8	(7.9)	
	RT after IPP	11	(4.3)	0	-	11	(10.9)	
RT Type	***EBRT***	62	(24.5)	0	-	62	(61.4)	N/A
	Brachytherapy	15	(5.9)	0	-	15	(14.9)	
	EBRT + Brachytherapy	2	(0.8)	0	-	2	(2.0)	
	Unknown	22	(8.7)	0	-	22	(21.8)	
	None	152	(60.1)	152	(100.0)	0	-	
RT Dose (rads)		7020	6660-7800	-	-	7020	6660-7800	N/A
RP Year		2006	2003-2009	2006	2003-2008	2008	2002-2009	0.801
RT Year		2008	2004-2011	-	-	2008	2004-2011	N/A
IPP Year		2011	2009-2014	2011	2009-2014	2011	2009-2014	0.240
IPP Type	***AMS***	214	(84.6)	133	(87.5)	81	(80.2)	0.277
	Coloplast	30	(11.9)	15	(9.9)	15	(14.9)	
	Unknown	9	(3.6)	4	(2.6)	5	(5.0)	
Prior AUS		32	(12.6)	21	(13.8)	11	(10.9)	0.493
Prior Other Incontinence Procedure		13	(5.1)	8	(5.3)	5	(5.0)	0.912
Dual Implant		65	(25.7)	48	(31.6)	17	(16.8)	0.009

RT = radiation therapy; BMI = body mass index; CCI = Charlson Comorbidity Index; RP = radical prostatectomy; IPP = inflatable penile prosthesis; EBRT = external bean radiation therapy; AMS = Ameircan Medical System; AUS = artificial urinary sphincter

Table 2. Baseline characteristics comparing inflatable penile prosthesis patients by receipt of any radiation therapy.

	Receipt of Radiation[1]				
	Control (N=148)	(%)	Any RT (N=87)	(%)	p-value
Any Complication	17	(11.5)	16	(18.4)	0.141
Infection	2	(1.4)	4	(4.6)	0.128
Erosion	5	(3.4)	1	(1.1)	0.296
Migration	2	(1.4)	1	(1.1)	0.894
Malfunction	8	(5.4)	8	(9.2)	0.265
Other	1	(0.7)	3	(3.4)	0.113
Revision Surgery	15	(10.1)	15	(17.2)	0.115
	Timing of Radiation[2]				
	Prior to IPP (N=79)	(%)	After IPP (N=8)		p-value
Any Complication	14	(17.7)	2	(25.0)	0.613
Infection	4	(5.1)	0	0.0	0.515
Erosion	1	(1.3)	0	0.0	0.749
Migration	1	(1.3)	0	0.0	0.749
Malfunction	6	(7.6)	2	(25.0)	0.104
Other	3	(3.8)	0	0.0	0.575
Revision Surgery	13	(16.5)	2	(25.0)	0.542
	Prior AUS Status[1]				
	No (N=208)	(%)	Yes (N=27)	(%)	p-value
Any Complication	29	(13.9)	4	(14.8)	0.900
	Receipt of a Dual Implant[1]				
	No (N=173)	(%)	Yes (N=62)	(%)	p-value
Any Complication	24	(13.9)	9	(14.5)	0.902
	IPP Type[1]				
	AMS (N=198)	(%)	Coloplast (N=29)	(%)	p-value
Any Complication	25	(12.6)	4	(13.8)	0.860

AUS = artificial urinary sphincter; IPP = inflatable penile prosthesis

[1]18 patients had incomplete data on complications and were excluded; 8 additional patients had incomplete data on IPP type and were excluded from comparison of complications by device type

[2]14 patients had incomplete data on complications and were excluded

Table 3. Comparisons of complications and need for revision surgery across various strata of patient characteristics.

both groups had > 85% rates of a functional prosthesis after 5 years. In a multivariable Cox regression model to control for potential confounders, RT remained unassociated with an increased rate of revision (HR: 1.07; CI 0.47-2.46), Table 5.

Discussion

In this study, we report surgical outcomes comparatively in a large contemporary cohort of patients with exposure to pelvic RT before or after IPP placement and a control group consisting of patients who underwent IPP implantation for post prostatectomy erectile dysfunction without exposure to RT. There was no significant difference in IPP surgical complications between the RT and control groups. In multivariable models, exposure to radiation did not increase the rate of complication from IPP surgery nor the rate of needing revision surgery.

External beam and implantable seed radiation therapies are established treatment options for organ confined prostate cancer and generally work by inducing apoptosis in cancerous cells. Despite improvements in radiation techniques affording less peripheral tissue damage, ED continues to be a common side effect of pelvic RT.[9] Patients undergoing pelvic RT are infrequently counseled on the sexual side effects of this treatment.[10] Tal et al reported on a national database review of 68,558 subjects who underwent radiotherapy or surgery for prostate cancer and reported that penile prosthesis utilization rate was only 0.3% in the RT group compared to 2.3% in the surgery group.[11] Although IPP implantation is generally considered the preferred treatment option for men with refractory ED

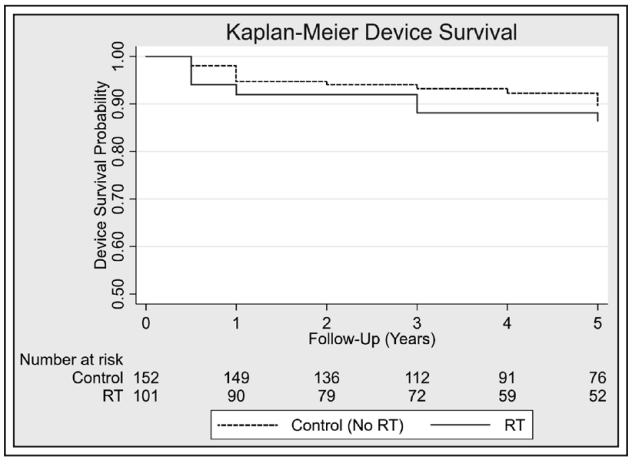

Figure 1. Kaplan Meier inflatable penile prosthesis device survival curve.

		OR	95%CI Low	95%CI High	p-value	OR	95%CI Low	95%CI High	p-value
		Univariable				Multivariable			
Control		REF	-	-	-	REF			
Any RT		1.74	0.83	3.64	0.145	1.31	0.55	3.12	0.540
Age	**(per year)**	0.98	0.94	1.02	0.277	1.00	0.94	1.05	0.885
CCI	**(per 1)**	1.17	0.91	1.51	0.214	-	-	-	-
CCI	**≤4**	REF	-	-	-	REF	-	-	-
	5-6	0.92	0.37	2.28	0.860	0.67	0.24	0.19	0.436
	≥7	1.60	0.51	5.00	0.418	0.80	0.20	3.23	0.750
BMI	**(per 1)**	1.07	1.00	1.15	0.064	-	-	-	-
BMI	**<25**	REF	-	-	-	REF	-	-	-
	25-29.9	0.63	0.20	1.96	0.424	0.65	0.20	2.07	0.463
	30-34.9	1.15	0.33	4.03	0.824	1.08	0.30	3.90	0.903
	≥35	2.58	0.67	10.04	0.170	2.13	0.49	9.22	0.314
Prior AUS		1.07	0.35	3.33	0.902	1.24	0.37	4.12	0.725
Dual Implantation		1.05	0.46	2.41	0.900	1.70	0.68	4.26	0.259
IPP Year		0.87	0.78	0.97	0.009	0.92	0.80	1.05	0.225

OR = odds ratio; RT = radiation therapy; CCI = Charlson Comorbidity Index; BMI = body mass index; AUS = artificial urinary sphincter; IPP = inflatable penile prosthesis

Table 4. Logistic regression models evaluating associations with developing a complication after placement of an inflatable penile prosthesis.

		HR	95%CI Low	95%CI High	p-value	HR	95%CI Low	95%CI High	p-value
		Univariable				Multivariable			
Control		REF	-	-	-	REF	-	-	-
Any RT		1.35	0.65	2.81	0.425	1.07	0.47	2.46	0.872
Age	**(per year)**	1.00	0.96	1.04	0.967	1.00	0.95	1.05	0.960
CCI	**(per 1)**	1.04	0.82	1.33	0.722	-	-	-	-
CCI	**≤4**	REF	-	-	-	REF	-	-	-
	5-6	0.85	0.35	2.06	0.716	0.75	0.28	1.97	0.555
	≥7	0.95	0.30	3.01	0.928	0.72	0.18	2.85	0.645
BMI	**(per 1)**	1.06	0.99	1.13	0.094	-	-	-	
BMI	**<25**	REF	-	-	-	REF	-	-	-
	25-29.9	1.43	0.40	5.11	0.582	1.33	0.37	4.77	0.657
	30-34.9	1.31	0.31	5.50	0.709	1.27	0.30	5.35	0.745
	≥35	3.25	0.81	13.08	0.096	3.07	0.71	13.30	0.133
Prior AUS		0.98	0.34	2817.00	0.964	1.10	0.37	3.32	0.864
Dual Implantation		1.30	0.57	2.96	0.526	1.62	0.68	3.83	0.273
IPP Year		0.99	0.88	1.10	0.801	1.03	0.89	1.20	0.684

HR = hazard ratio; RT = radiation therapy; CCI = Charlson Comorbidity Index; BMI = body mass index; AUS = artificial urinary sphincter; IPP = inflatable penile prosthesis

Table 5. Cox proportional hazards regression models evaluating risk factors for revision surgery among patients receiving inflatable penile prosthesis placement.

and is associated with improved patient and partner satisfaction, these data suggest a general reluctance or at least some uncertainty among urologists to offer IPP in this patient population.

Limited small clinical studies and case reports have suggested that exposure to RT for prostate cancer increases complication rates from IPP implantation.[4-6] Dobucq et al reported on 43 patients with a history of pelvic RT undergoing IPP and reported no infections or erosions, though this included a heterogeneous population of patients undergoing semi-rigid, 2-piece, and 3-piece IPP.[2] More recently, Loh-Doyle et al reported on 78 RT patients who underwent exclusively 3-piece IPP (AMS 700; Boston Scientific, Malborough, MA, USA) implantation via an infrapubic approach and concluded no increased risk of infection, erosion, or mechanical failure when compared to the global literature.[8] Golan et al queried The Surveillance, Epidemiology, and End Results (SEER)-Medicare Database for patients who underwent radiation or surgery for prostate cancer and subsequent 2 or 3-peice IPP implantation.[7] They reported no significant difference in 90 day, 1 year, and 3 year re-operation rates between the RT and surgery groups. In these more recent studies, the authors acknowledged the inherent limitation of studies utilizing national databases, as well as lack of a control group, incomplete data on type and dose of radiation, as well as inability to control for pertinent risk factors.

Our literature review revealed no previous large clinical study of patients with exposure to pelvic RT undergoing 3-piece IPP implantation compared to a control group, in which multivariate analysis of a number of relevant risk factors was done. Our results were generally comparable to more recent studies. The overall complication rate was 18.4% in the RT group compared to 11.5% in the control group, though this was not statistically significant ($p = 0.141$). Timing of radiation, prior AUS status, co-implantation of an AUS, and brand of prosthesis were not associated with increased rates of complications. On multivariate logistic regression analysis, neither type nor dose of radiation was associated with increased risk of complications. Device survival was comparable between both the RT and control groups.

We feel that IPP implantation is an acceptable treatment option for patients with a history of pelvic RT and refractory ED. Our study shows that these patients can be safely offered the procedure without significant increase in complication or need for revision compared to patients not exposed to RT. Proper patient selection, medical optimization prior to surgery, and meticulous technique remain paramount for all IPP surgical patients.

Our study does have certain limitations, including its retrospective design as well as inclusion of a relatively small amount of patients, although it is the largest clinical study to our knowledge to address this specific topic. The study also involved a single teaching institution and participation of various surgeons and trainees of all levels in surgeries. The median follow up was 5 years and may not account for all late complications from IPP surgery.

Conclusion

Pelvic RT is a well-accepted treatment option for patients with organ confined prostate cancer and other pelvic malignancies. This study shows no statistically significant increased risk for device complication in patients exposed to pelvic RT with a > 85% rate of freedom from revision surgery at 5 years. These findings support the use of IPP in men with a history of RT and refractory ED. □

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