Impact of radiotherapy for localized prostate cancer on bladder function as demonstrated on urodynamics study: A systematic review

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Cite as: Yao H.H-I, Hoe V, Shamout S, et al. Impact of radiotherapy for localized prostate cancer on bladder function as demonstrated on urodynamics study: A systematic review. *Can Urol Assoc J* 2021 June 22; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.7265

Published online June 22, 2021

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Abstract

Introduction: This study aimed to describe the effects of bladder function following radiotherapy for localized prostate cancer by performing a systematic review on studies reporting on urodynamic findings after radiotherapy.
Methods: This systematic review was conducted in accordance with PRISMA guidelines. The review protocol was registered at PROSPERO (CRD42021229037). A systematic search was conducted using PubMed, Cochrane Library, Scopus, and OVID Embase. Studies were included if they involved men who underwent urodynamic studies following radiotherapy for localized prostate cancer. A total of 798 articles were screened and five articles included. A qualitative analysis was performed.
Results: Bladder compliance appears to be impaired following radiotherapy, especially with longer followup. Impaired bladder compliance was reported in 18.8–62.5% of patients following radiotherapy. Bladder capacity was found to be statistically significantly lower following radiotherapy compared to pre-radiotherapy, and when compared with patients who did not undergo pelvic radiotherapy. Bladder outlet obstruction (BOO) persists post-radiotherapy in most patients at three and 18 months post-radiotherapy. De novo detrusor overactivity (DO) of 13.3% has been reported at 18 months post-radiotherapy. This review is limited by the absence of level I/II studies.
Conclusions: Radiotherapy for localized prostate cancer results in decreased bladder compliance and capacity demonstrated on urodynamic studies. Resolution of BOO appears

less likely in comparison to series on radical prostatectomy. De novo DO may develop following radiotherapy, especially with longer followup. With only low level of evidence studies available at present, further high-quality, prospective studies are important to elucidate the impact of radiotherapy on bladder and urethral function.

Introduction

Prostate cancer is the second most commonly diagnosed cancer in men[1]. Curative management options for localized prostate cancer include radical prostatectomy (RP) and radiotherapy. Conventional radiotherapy techniques such as external-beam radiotherapy and low-dose brachytherapy have demonstrated similar efficacy to RP with regard to oncologic outcomes[2]. Both RP and radiotherapy as curative treatment provide patients with a favourable long-term overall and cancer-specific survival rate[3]. With a prolonged survival following curative treatment, achieving optimal functional and quality-of-life (QOL) outcomes are important. The trifecta of cancer control, urinary continence and erectile function are heavily studied[4], but bladder function less frequently so[5].

Lower urinary tract symptoms (LUTS) are a well-known side effect of radiotherapy for prostate cancer, due to genitourinary toxicity[5]. There is a paucity of data on bladder function following radiotherapy for prostate cancer. The most objective method to determine changes in bladder function is with urodynamic studies. This study aims to determine the effects of bladder function following radiotherapy treatment of prostate cancer by performing a systematic review on urodynamic findings before and after radiotherapy. The results of this study will assist clinicians in the counselling of patients regarding the effect of radiotherapy treatment of prostate cancer on bladder function outcomes post-radiotherapy.

Methods

This systematic review was conducted in accordance with the PRISMA guideline. The review protocol was registered at PROSPERO (https://www.crd.york.ac.uk/prospero/): registration number (CRD42021229037).

The study cohort include patients with localized prostate cancer treated with radiotherapy. This systematic review included patients who were treated both in the primary setting as well as adjuvant or salvage setting following prostatectomy. Studies were eligible to be included if there were urodynamics study performed following radiotherapy to assess the impact of radiotherapy on bladder function. Articles were excluded if they were non-English articles, non-full text articles, review articles and other article types with no original data.

The primary outcome assessed in this study is the rate of urodynamic changes (detrusor overactivity, bladder compliance, maximum cystometric capacity, bladder contractility and bladder outlet obstruction). As there is significant heterogeneity of the underlying patient population across the study, and incomplete reporting of each of the

outcomes for different studies, a quantitative analysis could not be performed. A descriptive qualitative analysis is reported.

Systematic search was conducted independently by two investigators using PubMed, Cochrane library, Scopus and OVID Embase on 16th of October 2020. The complete search protocol with inclusion and exclusion criteria are listed in Figure 1. Abstracts were screened independently by two investigators to identify articles to be included. Full-text articles were reviewed if eligibility to be included in the review was not able to be determined from the title and abstract. Discrepancy of assessment between investigators were resolved following a discussion to reach a consensus. Risk of bias assessments were performed individually by two investigators using the National Heart, Lung, and Blood Institute Study Quality Assessment Tools[6]. Data were collected into an electronic data collection form, and included baseline demographics data, method of radiotherapy, dose and fraction of radiotherapy, baseline disease characteristics, patient reported outcome measures (PROMs) data at baseline and follow-up, urodynamics data at baseline and following radiotherapy.

Results

A total of 798 articles were screened to assess for eligibility. After removing 75 duplicates, 723 articles were screened against title and abstract and 19 articles assessed for full-text eligibility. Five of the nineteen articles were eligible to be included in the final review[7-11]. Reasons for exclusion are listed in Figure 1. Two of the articles came from the same cohort of patients with different lengths of follow-up, and therefore were analysed together as one study. The final number of studies included was four, two retrospective cohort study, one retrospective pre-post study published in two articles with different follow-up times, and one case series. Only low-level evidence (3 or 4) studies were found in the literature for this systematic review. On risk of bias assessment, two articles were found to have a low risk of bias and three articles were found to have at least a moderate risk of bias for the type of study conducted.

Baseline demographics

One of the four studies included both prostate cancer and colorectal patients, with most of the patients having radiotherapy for prostate cancer (n=58/99)[10]. This study also had a control group of non-radiotherapy patients for comparison[10]. One study involved patients with primary curative radiotherapy only[7, 8]. Another study included patients following salvage radiotherapy following RP[9]. The final study included patients following adjuvant radiotherapy and compared with patients who underwent RP alone as control[11]. The number of prostate cancer radiotherapy patients in each study ranged from 10 to 58 (Table 1). The sum total of prostate cancer radiotherapy patients included in this systematic review was 100. The median age of patients at time of radiotherapy ranged from 64.9 to 72 years. Prostate volume was not reported in all studies. Prostate cancer disease characteristic was reported in only two articles that belonged to the same study (Table 1).

External beam radiotherapy was used in all studies. Two studies used 3D conformal therapy[9, 10], one study used 4 field box technique[7, 8], and one study included patients with

both techniques[11]. The dose of radiation ranged from 59Gy to 72Gy[7-9, 11]. One study included colorectal cancer patients and reported the radiation dose to range between 24-78Gy[10]. The authors of that study did not specify the dose used in prostate cancer, but it is likely that the dose would be in the higher end of the reported range when used to treat prostate cancer in keeping with standard practice. Only one study reported the dose of bladder exposure to the radiation with a median of 81.7ml of bladder within 80% of radiation isodose and median of 134.8ml within 50% of radiation isodose[7, 8]. Bladder was filled during this study in order to reduce the amount of bladder exposure[7, 8].

Symptoms and PROMs

Only one study reported changes to symptoms and PROMs compared with baseline (Table 2)[7, 8]. In this study, the baseline median International Prostate Symptoms Score (IPSS) was 7 (range 1-22), the median IPSS Quality of Life (QoL) score was 1.5 (range 0-5), and the baseline median urinary frequency per 24 hours was 8.5 (range 4-14) [7, 8]. Urgency was reported in 62.5% of men and urge urinary incontinence in 25% of men prior to radiotherapy[7, 8]. Median urinary frequency, IPSS and IPSS QoL scores were not statistically significantly different at 3 and 18 months compared with baseline[7, 8]. Overall, the percentage of men with urgency symptoms were worse at 3 months following radiotherapy as 31.3% of men developed de novo urgency, 43.8% of men had persistent urgency and only 18.8% had de novo resolution of urgency symptoms[8]. Similarly, the percentage of men with urge urinary incontinence was higher at 3 months, with 18.8% developing de novo urge urinary incontinence, 25% of men experiencing persistent urge urinary incontinence and no de novo resolution following radiotherapy[8]. These rates remain largely unchanged at 18 months compared with 3 months post-radiotherapy[7, 8]. Only one other study reported PROMs outcome and found 62.5% of men to have moderate or severe Danish Prostatic Symptom Score (DAN-PSS) at median of 7.7 years following salvage radiotherapy[9].

Bladder outlet obstruction

Changes to urodynamics BOO were reported by only one study[7, 8]. The rate of BOO demonstrated on urodynamics at baseline was 81.3%[7, 8]. BOO is largely persistent with 75% of patients still experiencing BOO at 3 months and 60% of men at 18 months[7, 8]. 20% of men experience de novo resolution of BOO following radiotherapy at 18 months[7]. A small percentage (6.3%) of men experienced de novo BOO at 3 months but this is resolved by 18 months[7, 8]. The maximum flow rate and post void residual does not appear to be impacted following radiotherapy at 3 and 18 months[7, 8]. Ervandian et al. did not compare BOO rates with baseline and reported a significant rate of BOO of 43.8% at median of 7.7 years following salvage radiotherapy with an additional 25% of men unable to void with the presence of a urodynamics catheter[9]. Similarly, the reported mean Qmax is poor at 9.6 to 11.4 ml/s[9].

Detrusor overactivity

Changes to the frequency of urodynamics DO were reported by only one study[7, 8]. The rate of DO at baseline was reported to be high at 56.3% in keeping with the significant symptoms of

urgency and urge urinary incontinence reported by the same cohort of patients[7, 8]. This is in the setting of a baseline BOO of 81.3% suggesting that concurrent benign prostate hyperplasia (BPH) is likely to play a role in the secondary DO[7, 8]. Overall, the rate of DO remained unchanged following radiotherapy at 3 months, and slightly worse at 60% at 18 months with 13.3% of men having developed de novo DO following radiotherapy[7, 8]. Another study with no baseline urodynamics reported rates of DO to be 37.5% at median of 7.7 years following radiotherapy[9].

Bladder compliance

Only one study compared bladder compliance changes following radiotherapy to baseline[7, 8]. This study reported only a small percentage (12.5%) of patients to have decreased bladder compliance at baseline[7, 8]. Overall, the percentage of patients with decreased compliance was only slightly worse at 3 months at 18.8%[8]. This progressively worsened with time, and at 18 months following radiotherapy 33.3% of patients experienced a decreased bladder compliance[7]. Ervandian et al. did not compare bladder compliance with baseline but reported a high rate of impaired bladder compliance in 62.5% of men at median of 7.7 years following salvage radiotherapy[9]. Mendez-Rubio et al. compared the rate of decreased bladder compliance between patients who did and did not undergo pelvic radiotherapy and found pelvic radiotherapy to be statistically significantly predictor of decreased bladder compliance on univariate and multivariate analyses[10].

Bladder capacity

Two studies compared mean maximum cystometric capacity (MCC) post-radiotherapy with baseline[7, 8, 11], and both reported a reduction in MCC following radiotherapy. One study reported statistically significant reduction in mean MCC from 422.6ml to 352.9ml at 3 months and further reduced to 328.6ml at 18 months[7, 8]. The same study also demonstrated bladder volume at first sensation and strong desire to be lower following radiotherapy at 18 months[7, 8]. Another study reported MCC reduced from 322ml to 269ml at 3-22 months following radiotherapy[11]. Given there was only 4 patients in this pre-post analysis, statistical significance was not found[11]. This study involved patients who had adjuvant radiotherapy (n=10) and compared the urodynamics finding with a group of patients who only had RP (n=13) and found no difference in the MCC on follow-up[11]. Mendez-Rubio et al. compared patients who had pelvic radiotherapy with patients who did not and found mean bladder volume at first desire and MCC to be both statistically significantly worse compared with control[10]. The mean MCC in radiotherapy patients was 175ml compared with 236ml in control group ($p<0.001$)[10]. Ervandian et al. did not compare MCC with baseline but at median of 7.7 years following salvage radiotherapy the mean MCC appear to be low at 297.8ml[9].

Discussion

This systematic review highlights the paucity of research in the currently literature examining the bladder function for patients following radiotherapy for localised prostate cancer. From the limited literature available, it appears that radiotherapy results in impaired bladder compliance and decreased bladder capacity. Resolution of BOO appears to be less than

studies involving RP patients[12]. De novo DO may develop following radiotherapy, especially with longer follow-up. As LUTS have a potentially significant impact on QoL, it is important to counsel patients adequately prior to consideration of curative treatment options for prostate cancer. The findings of this review emphasises the importance of adequate pre-treatment assessment of LUTS in addition to post-treatment evaluation to identify patients who may benefit from treatment to improve their QoL.

Bladder compliance appears to worsen following radiotherapy[7, 8, 10], especially with time[7, 8]. This is consistent with the mechanism of radiation induced damage, which often manifests at a delayed time[13]. Radiotherapy utilises ionizing radiation to destroy tumour cells by increasing production of free radicals and reactive oxygen species (ROS) that damage structural proteins and genetic material, ultimately leading to cell death[14]. The effects of radiation are however not limited to malignant cells, causing collateral damage to surrounding healthy tissues. Radiation induced damage to vascular endothelial cells generates a reserve of long-lasting free radicals and ROS with subsequent inflammation, vascular hyperplasia, perivascular fibrosis and end vascular occlusion[14]. These pathological changes occur by 6-12 months following radiotherapy, but the resulting bladder fibrosis and degeneration of bladder wall that occurs secondary to vascular ischaemia of the bladder wall is generally seen months to years after radiotherapy[13]. This ultimately results in decreased bladder compliance and contraction[14]. The high rate of poor bladder compliance seen in salvage radiotherapy is likely attributable more to radiotherapy than to RP, with a previous systematic review having shown that although bladder compliance is initially impaired following RP, this tends to recover with time[12, 15].

The mechanism for reduction in bladder capacity following radiotherapy as demonstrated in the studies by Do et al., Choo et al. and Mendez-Rubio et al. is likely similar to previously described for decreased bladder compliance[7, 8, 10]. The study by Presti et al. comparing RP and adjuvant radiotherapy with RP alone found no difference in MCC, but the numbers are likely too small to detect a difference[11]. Furthermore, RP itself is a confounder as it has been shown to reduce bladder compliance and contractility, which may be related to decentralisation of the bladder from its mobilisation during prostatectomy, bladder denervation due to disruption of branches of the pudendal nerve, post-operative inflammatory changes and geometric bladder wall alteration[12]. This effect of RP may recover over time, with Giannantoni et al. showing an improvement in bladder compliance at 36 months following RP[15]. There are no long-term studies to demonstrate similar recovery in patients following radiotherapy. With the proposed mechanism secondary to fibrosis of the bladder, the reversibility of impaired bladder compliance and MCC following radiotherapy seems less likely. Further longer-term follow-up studies are required to elucidate this.

Prostate swelling caused by radiation is resolved in the majority of patients by 3 months, with only a small number experiencing de novo BOO that is ultimately resolved by 18 months[7, 8]. BOO does not appear to be worse at 3 and 18 months post-radiotherapy, with Qmax and PVR similarly unchanged[7, 8]. In contrast to a BOO improvement rate of 20-59.3% following RP[12], resolution of BOO post radiotherapy is not as significant. Unlike RP, BPH can persist following radiotherapy. Clinically, this may be ameliorated by medical or surgical

treatment of BOO before or after radiotherapy as per usual indications for concurrent BPH[16]. A high rate of BOO reported by Ervandian et al. following salvage radiotherapy is likely secondary to the combined effects of both RP and radiotherapy[9]. The majority of patients in that cohort, underwent open RP, which is known to be associated with a higher rate of vesicourethral anastomotic stenosis (VUAS) compared to robot-assisted RP[17]. Furthermore, radiotherapy has been known to make VUAS worse and cause urethral stricture disease[18]. As such, it Is possible that these patients have a higher rate of BOO secondary to urethral stricture and VUAS complications as a result of receiving both therapies.

OAB symptoms appear to be more common and severe following radiotherapy than after RP[5]. Similarly, radiotherapy does not result in the same degree of improvement of DO as seen following RP[12]. DO appears to remain largely the same and possibly slightly worse at 18 months[7, 8]. Two possible explanations are thought to account for this. Firstly, radiotherapy may result in radiation cystitis which is associated with lower urinary tract symptoms[14, 19]. It is plausible that with longer follow-up the bladder effects secondary to radiation manifests themselves more prominently, as demonstrated in a study reporting the rate of DO following salvage radiotherapy to be as high as 37.5% at 7.7 years[9]. Secondly, a significant portion of patients' DO at baseline is secondary to BOO from BPH, and unlike RP whereby BOO is relieved following removal of the prostate gland, radiotherapy does not resolve BOO to lead to the secondary resolution of DO.

The systematic review is limited by the low level of evidence in the current literature and the scarce number of studies published in this area. The majority of studies had a small number of participants. Furthermore, incomplete reports of important parameters and outcomes measures examined in this review were common throughout studies. PROMs data on LUTS following radiotherapy was poorly reported in conjunction with urodynamic results. Whilst studies have shown good correlation between symptoms and urodynamic findings, reported rates of OAB symptoms may be higher than in urodynamic studies[20]. Additionally, patients may also have urodynamic changes suggestive of BOO without clinical significance, due to the presence of a transurethral transducer obstructing flow and exacerbating the underlying condition. Future studies of urodynamics post-radiotherapy should therefore be performed in conjunction with PROMs. Finally, the absence of brachytherapy patient cohorts in the literature on this topic, limits extrapolation of the findings in this review to brachytherapy patients. Overall, given the current level of evidence available in the literature, it is difficult to draw any strong conclusions.

Conclusions

Radiotherapy for localised prostate cancer results in impaired bladder compliance and decreased bladder capacity as demonstrated on urodynamics studies. Resolution of BOO appears less likely in comparison to case series on radical prostatectomy. De novo DO appear to develop following radiotherapy, especially with longer follow-up. With only low level of evidence studies available at present, further high-quality prospective studies are important to elucidate the impact of radiotherapy on bladder function.

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Figures and Tables

Fig. 1. Results of search strategy using PubMed, Scopus, EMBASE, and Cochrane.

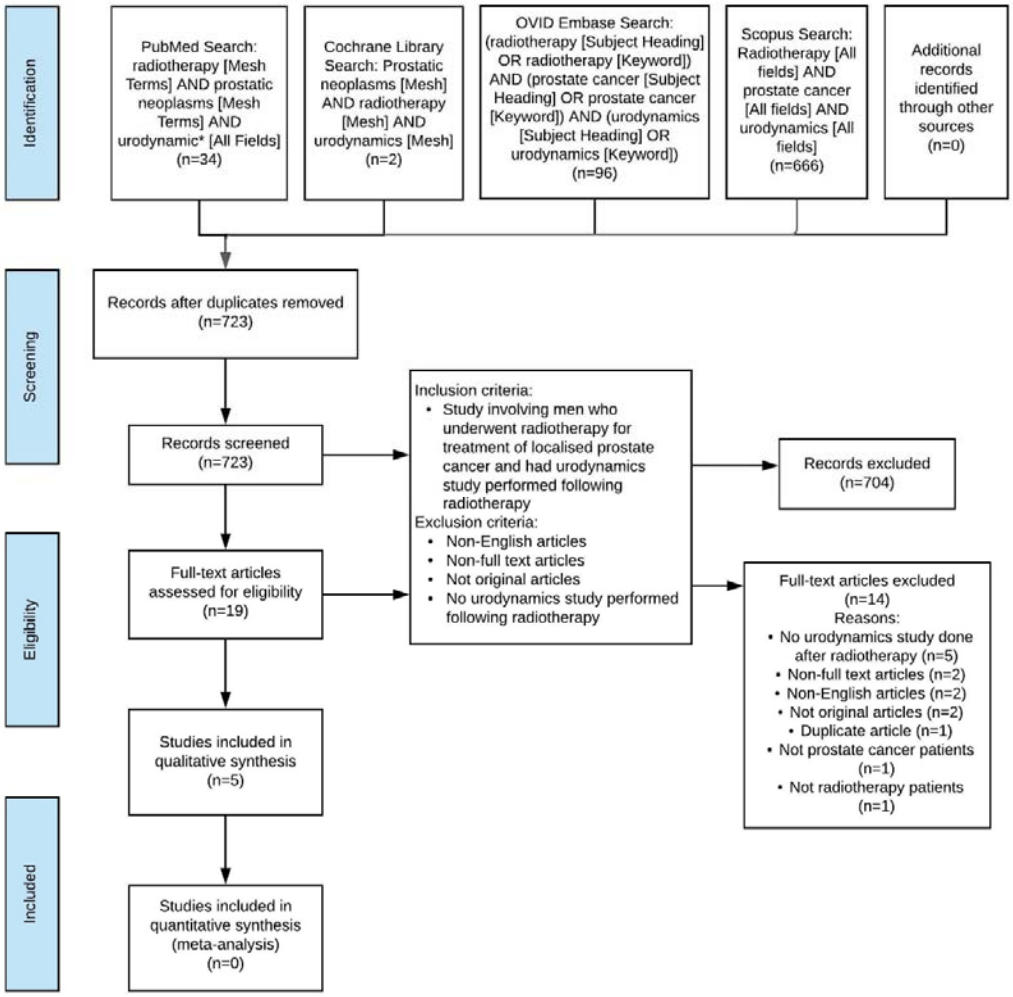

Table 1. Baseline disease and treatment characteristics of studies examining the impact of radiotherapy for prostate cancer on urodynamics findings

Author	Study type	Number	Age	Initial PSA (ng/mL)	Biopsy grade	Clinical T Stage	Method of RT	Technique details	Dose/fractions	Bladder within radiation field
Ervandian et al. 2018[9]	Case series	RRP + salvage RT (n=15); RARP + salvage RT (n=1)	Median age at RRP 62.5 (52.8-72.1) and median age at RT 64.9 (56.2-73.4)	Pre-RRP PSA: <10 in 3, 10-20 in 9, >20 in 4. Pre-RT PSA: 0.2 in 1, 0.2-0.5 in 2, >=0.5 in 11, unknown in 2	N/A	N/A	EBRT	3D conformal therapy	68 Gy/34 fractions (except 1 patient had 72 Gy/36 fractions)	N/A
Mendez-Rubio et al. 2015[10]	Retrospective cohort study	Total number (n=99); Primary RT (n=49); Adjuvant RT (n=50); Prostate cancer (n=58); Colorectal cancer (n=41)	Mean 69 +/- 8.5	N/A	N/A	N/A	EBRT	3D conformal therapy	24-78 Gy / 12-39 fractions at daily dose of 2Gy and between 2-8 weeks of treatment	N/A
Do et al. 2002[8] and Choo et al. 2002[7]*	Pre-post study	16/17 completed the study	Median 72 (Range 56-77)	Median 8.55 (Range 1.1-49.7)	Median 7 (6-8)	T1c (n=3); T2 (n=12); T3 (n=1)	EBRT	Four-field box technique and high energy photons (18 or 23 MV)	66 Gy / 33 fractions to 70 Gy / 35 fractions	Within 100% of radiation isodose = median 0.9 (0-19.5)% and median 4.1 (0-36.3)mL; Within 80% of radiation

										isodose = median 30.6% and median 81.7 (43.4-151)mL; Within 50% of radiation isodose = median 60.6% and median 134.8 (72-500)mL
Presti et al. 1996[11]	Prospective cohort study	Adjuvant RT after RRP (n=10); RRP only (n=13)	N/A	N/A	N/A	N/A	EBRT	3D conformal therapy (n=8); 4-field standard RT (n=2)	Mean 6328 cGy (range 5940-6500 cGy)	N/A

*These two studies were from the same population with different lengths of followup. EBRT: external beam radiation therapy; MV: megavolts; PSA: prostate-specific antigen; RARP: robot-assisted radical prostatectomy; RRP: retropubic radical prostatectomy; RT: radiotherapy.

Table 2. Studies examining the impact of radiotherapy for prostate cancer on overactive bladder symptoms, patient-reported outcome measures, and urodynamics findings

Author	Patient selection	Changes in overactive bladder symptoms	Changes in PROMs	Timing of UDS	Bladder compliance	Detrusor overactivity	Bladder capacity	Bladder outlet obstruction
Ervandian et al. 2018[9]	89 patients SRT patients eligible; 52 invited for study; 16 consented for per-protocol urodynamics	N/A	N/A	Median time from SRT = 7.7 years (range 5.8-10)	Low in 10 (62.5%) - defined as <30-40ml/cmH2O	Detrusor overactivity = 6 (37.5%)	297.8 +/- 28.3 mL	7 (43.8%) with 4 unable to void (25%)
Mendez-Rubio et al. 2015[10]	Not stated as per-protocol urodynamics or urodynamics performed for symptoms	N/A	N/A	Mean 4.7 years (SD 4.07 years)	Rates not reported; pelvic radiotherapy shown to be a predictor of decreased compliance on univariate and multivariate analysis	Rates not reported; pelvic radiotherapy not found to be a predictor of detrusor overactivity	175 +/- 105.4 (c.f. 236 +/- 128.0 in control group*, p=0.000)	N/A
Do et al. 2002[8]	Per-protocol urodynami	3 months: De novo urgency = 31.3% (n=5/16); De novo	3 months = mean (SEM) change for	3 months and 18 months	3 months: De novo decreased compliance =	3 months: De novo DO = 12.5% (n=2); De	3 months: Supine mean (SEM) change is	3 months: De novo BOO = 6.3% (n=1); De

and Choo et al. 2002[7]#	cs for all eligible patients who consented	resolution of urgency = 18.8% (n=3/16); Persistent urgency = 43.8% (n=7/16); De novo urge incontinence = 18.8% (n=3/16); De novo resolution of urge incontinence = 0% (n=0/16); Persistent urge incontinence = 25% (n=4/16) 18 months: De novo urgency = 33.3% (n=5/15); De novo resolution of urgency = 20% (n=3/15); Persistent urgency = 40% (n=6); De novo urge incontinence = 20% (n=3/15); De novo resolution of urge incontinence = 0% (n=0/15); Persistent urge incontinence = 20% (n=3/15)	urinary frequency = 1.56 (1.04); for IPSS = 1.38 (1.81); for QoL = 0.06 (0.39); Statistically not different from baseline 18 months = Mean (SEM) change for urinary frequency = 0.67 (0.81); for IPSS = 0.4 (1.63); for QoL = 0 (0.29); Statistically not different from baseline		18.8% (n=3); De novo resolution = 12.5% (n=2) 18 months: De novo decreased compliance = 26.7% (n=4/15); De novo resolution = 6.7% (n=1/15); Persistent decreased compliance = 6.7% (n=1/15)	novo resolution = 12.5% (n=2); DO persistent = 43.8% (n=7) 18 months: De novo DO = 13.3% (n=2/15); De novo resolution = 6.3% (n=1/15); DO persistent = 46.7% (n=7/15)	-70mL (29), p=0.028; Upright mean (SEM) change is -21mL (29), p=0.49 18 months: Supine mean (SEM) change is -100mL (20), p=0.0002; Upright mean (SEM) change is -54mL (23), p=0.035	novo resolution = 12.5% (n=2); BOO persistent = 68.8% (n=11) 18 months: De novo BOO = 0% (n=0/15); De novo resolution = 20% (n=3/15); BOO persistent = 60% (n=9/15)
Presti et al. 1996[11]	Not stated as per-protocol urodynamics or urodynami	N/A	N/A	3-22 months following adjuvant RT	N/A	N/A	Before RT = 322 +/- 116 mL; After RT = 269+/-75 mL	N/A

	cs performed for symptoms							

*Control group are patients who did not undergo pelvic radiotherapy. #These two studies were from the same population with different lengths of followup.
BOO: bladder outlet obstruction; DO: detrusor overactivity; IPSS: International Prostate Symptom Score; N/A: not available (i.e., not reported); PROMs: patient reported outcome measures; QoL: quality of life; RT: radiotherapy; SD: standard deviation; SEM: standard error of the mean; SRT: salvage radiotherapy; UDS: urodynamics study.

Supplementary Table 1. Risk of bias assessments using the National Heart, Lung, and Blood Institute Study Quality Assessment Tools

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Rater 1	Rater 2
Presti et al. 1996[11]*	Yes	No	CD	CD	No	Yes	Yes	Yes	Yes	Yes	Yes	CD	No	No	Fair	Fair
Mendez-Rubio et al. 2015[10]*	Yes	No	CD	CD	Yes	Yes	Yes	No	Yes	Yes	No	CD	CD	No	Fair	Fair
Ervandian et al. 2018[9]#	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes						Fair	Fair
Do et al. 2002[8]^	Yes	Yes	CD	No	No	Yes	Yes	CD	Yes	Yes	Yes	NR			Good	Good
Choo et al. 2002[7]^	Yes	Yes	CD	No	No	Yes	Yes	CD	Yes	Yes	Yes	NR			Good	Good

*Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies form used. #Quality Assessment Tool for Case Series Studies used.
^Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group used. CD: cannot determine; NR: not reported.