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CLINICAL INVESTIGATIONS

Late Urinary Toxicity and Quality of Life With Pelvic Radiation Therapy for High-Risk Prostate Cancer: Dose-Effect Relations in the POP-RT Randomized Phase 3 Trial

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Purpose: The POP-RT phase 3 randomized trial showed improved biochemical failure-free survival and metastasis-free survival with whole pelvic radiation therapy versus prostate-only radiation therapy for high and very high-risk prostate cancer, albeit with worse RTOG late urinary toxicity. We report updated late urinary adverse effects and bladder dose-effect relations within this trial.

Methods and Materials: Late urinary toxicity and the cumulative severity of each symptom during the follow-up period were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Bladder dosimetry in 5-Gy increments (V5, V10, V15, V65, V68Gy) in the approved radiation therapy plans was compared with urinary symptoms and overall grade 2+ toxicity. Potential factors influencing urinary toxicity were tested using multivariable logistic regression analysis. Updated urinary quality of life (QOL) scores were compared between the trial arms.

Results: Complete combined data for late urinary symptoms and dosimetry was available for 193 of 224 patients. At a median follow-up of 75 months, cumulative late urinary CTCAE grade 3 toxicity was low and similar for whole pelvic radiation therapy and prostate-only radiation therapy (5.2% vs 4.1%, P = .49), and grade 2 toxicity was 31.3% versus 22.7%, respectively (P = .12). Cumulative rates of each urinary symptom were similar between both arms. Multivariable

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Priyamvada Maitre and Guncha Maheshwari made equal contributions to this study.

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Data Sharing Statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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analysis with age at diagnosis, known diabetes, tumor stage, trial arm, prior transurethral resection of prostate, grade 2+ acute urinary toxicity, low bladder dose (V10Gy), and moderate bladder dose (V40Gy) did not identify any significant association with late urinary toxicity. Urinary QOL scores was similar between both the arms for all the symptoms.
Conclusions: During long-term follow-up, whole pelvic radiation therapy resulted in low (∼5%) and similar grade 3 cumulative urinary toxicity as prostate-only radiation therapy. The long-term patient-reported QOL scores were similar. No causative factors affecting the late urinary toxicity were identified.

Introduction

Prophylactic pelvic nodal irradiation during curative-intent radiation therapy for high- to very high-risk, node-negative prostate cancer was tested by the phase 3 randomized controlled trial Prostate-Only versus Whole-Pelvic Radiation Therapy (POP-RT).[1] Based on the large and clinically meaningful improvement in disease-free survival and metastasis-free survival at 5 years, whole pelvic radiation therapy (WPRT) has been accepted as the standard of care.[2] This improvement in outcomes comes with a modest increase in cumulative grade 2 late urinary toxicity, although it is not reflected in the patient-reported quality of life (QOL) scores.[3]

The lack of difference in acute and late gastrointestinal toxicity may be largely attributed to the rigorous bowel sparing achieved with daily image-guided intensity modulated radiation therapy (IG-IMRT) in this trial. However, the reasons for higher urinary toxicity reported previously are not obvious. Early analysis suggested that although the high dose (50-70 Gy) were similar between the 2 arms, the volume of bladder exposed to low and mid-range doses of 10 to 40 Gy was higher in the WPRT arm, which may have contributed to the increased urinary adverse effects.[3] The role of lower doses to the rest of the bladder is uncertain in the present literature.[4,5] Individual symptoms of late urinary toxicity, such as frequency, hematuria, or obstruction, vary in cause and management.[6] A detailed update of cumulative late urinary toxicity and patient-reported QOL with a focus on individual urinary symptoms was undertaken within the POP-RT trial to understand the potential contributory factors and bladder dose-effect relations.

Methods and Materials

The POP-RT trial (NCT02302105) enrolled patients who received a diagnosis of high- or very high-risk, node-negative, biopsy-proven prostate adenocarcinoma planned for curative-intent radiation therapy, randomizing to either prostate-only radiation therapy (PORT) or WPRT with at least 2 years of androgen deprivation therapy. All patients were treated with IG-IMRT to a moderately hypofractionated dose of 68 Gy in 25 fractions to the prostate, with simultaneous 50 Gy to the regional pelvic nodes below the aortic bifurcation in the WPRT arm. Follow-up continued at 3 to 6 monthly intervals with urinary and gastrointestinal toxicities assessed using the Radiation Therapy Oncology Group (RTOG) scale, and QOL with European Organization for the Research and Treatment of Cancer Core Quality of Life Questionnaire and Prostate Cancer Module measures at every visit. The complete trial protocol with details of treatment and follow-up assessments has been published previously.[1]

For this study, the incidence of each urinary symptom reported during follow-up after 3 months of radiation therapy completion was identified from trial records until December 2022. Late urinary toxicity included symptoms of frequency, urgency, dysuria, hematuria, incontinence, urinary obstruction, and noninfective cystitis. Cumulative severity of each symptom was graded as per the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. In this scale, all urinary symptoms are graded from 0 to 5, except dysuria graded as 0 to 1. Broadly, symptoms managed with invasive interventions, such as intravenous medications, hospitalization, or gross hematuria requiring transfusion, are classified as grade 3; and those limiting activities of daily living, requiring medical management on outpatient basis, an increase in the dose of existing medication for symptomatic worsening, or placement of urinary catheter are classified as grade 2. The highest severity of each symptom during the duration of follow-up was considered for assigning the worst grade of cumulative toxicity for the analysis. Because "noninfective cystitis" includes all other urinary symptoms, including nocturia, the worst grade for any urinary symptom was labeled as the worst grade of noninfective cystitis. This represented the cumulative grade of overall late urinary toxicity.

Patient-reported QOL scores for the urinary domain of PR-25 were updated and standardized to 0 to 100 linear scale according to the EORTC guidelines. Mean serial scores were compared between the arms using generalized linear mixed model with repeated measures. Missing scores were not imputed. A difference of ≥10 points between the mean QOL scores was considered clinically significant.

Bladder volume dosimetry in 5-Gy increments (V5, V10, V15,...V65, V68) was extracted from the trial database of approved radiation therapy plans, where V5 Gy represents the percentage volume of bladder receiving 5 Gy dose. Patients with incomplete records of late symptoms or unavailable dose-volume data were excluded from the present analysis. Patient and disease characteristics were summarized using descriptive statistics. Incidence of grade 2+ toxicities for each urinary symptom (grade 1 for dysuria) was compared between the trial

arms using the χ^2 test or Fisher exact test. Mean bladder dose-volume parameters were compared for cumulative grade 2+ toxicity for each urinary symptom by Student's *t* test.

Potential contributory factors for late urinary toxicity (cumulative grade 2+ yes/no) were tested with multivariable binary logistic regression analysis, including age at diagnosis, known diabetes mellitus, tumor stage, trial arm, prior transurethral resection of prostate (TURP), grade 2+ acute urinary toxicity, and bladder dosimetry as potential contributory factors. All the factors were tested in multivariable binary logistic regression analysis irrespective of the univariable analysis for each factor. A P value < .05 was considered statistically significant. All statistical analyses were performed using SPSS (IBM Inc), version 25.

Results

Of the total 222 patients enrolled in the POP-RT trial, 193 with complete dosimetric and follow-up data were eligible for analysis (PORT = 97, WPRT = 96; Fig. 1). Baseline characteristics of the study cohort were well-balanced between the 2 arms (Table 1). The majority (79%) of patients were locally advanced (stage ≥T3a), with nearly a third (29%) having undergone TURP before radiation therapy.

At an updated median follow-up of 75 months, no patient developed grade 4 CTCAE late urinary toxicity. Grade 3 urinary toxicity was observed in total 9 patients (WPRT = 5, 5.2%, PORT = 4, 4.1%, P = .49), similar in both the arms. Grade 2 toxicity was recorded in 52 patients (WPRT = 30, 31.3%; PORT = 22, 22.7%), also similar in both the arms. Comparison of urinary symptoms showed no significant difference for any symptom between the 2 arms (Fig. 2).

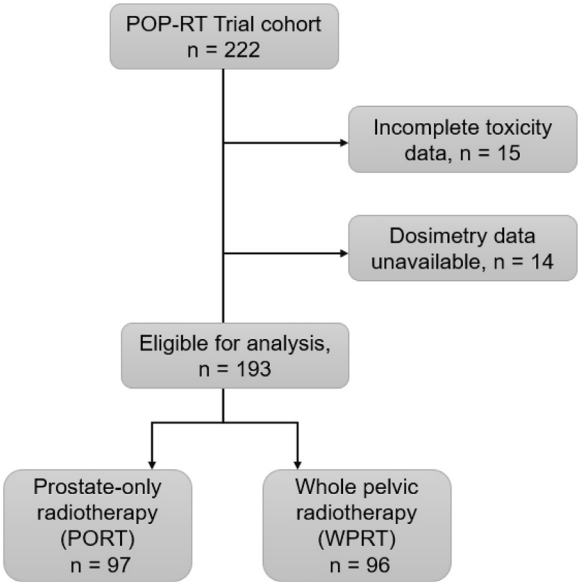


Fig. 1. Study cohort. *Abbreviation*: POP-RT = Prostate-Only versus Whole-Pelvic Radiation Therapy.

Table 1 Baseline characteristics

Characteristics	PORT (n = 97)	WPRT (n = 96)	Total (n = 193)	*P* value
Age, y (median, IQR)	66 (61-71)	66 (61-72)	66 (61-72)	.16
Diabetes mellitus				
Yes	30 (31%)	22 (23%)	52 (27%)	.21
No	67 (69%)	74 (77%)	141 (73%)	
TURP before radiation therapy				
Yes	27 (28%)	29 (30%)	56 (29%)	.72
No	70 (72%)	67 (70%)	137 (71%)	
Tumor stage				
T1	0	01 (1%)	01 (0.5%)	.59
T2	17 (18%)	23 (24%)	40 (21%)	
T3a	35 (36%)	28 (29%)	63 (33%)	
T3b	38 (39%)	36 (38%)	74 (38%)	
T4	7 (7%)	8 (8%)	15 (8%)	

Abbreviations: PORT = prostate-only radiation therapy; TURP = transurethral resection of prostate; WPRT = whole pelvic radiation therapy.

Comparison of long-term patient-reported urinary QOL scores showed the mean scores being similar between the trial arms during the updated follow-up period, with no clinically significant difference at any time (Fig. 3A). Additionally, comparison of mean QOL scores between the patients observed to have grade 2+ late urinary toxicity versus grade 0 to 1, showed no clinically significant difference at any time (Fig. 3B).

Evaluation of bladder dosimetry showed that the protocol-specified planning constraints for the bladder were achieved in both the arms. Expectedly, the mean volume of bladder receiving 5 to 50 Gy dose was higher with WPRT, with larger differences in the lower end of dose range (Fig. 4A). However, when the bladder dosimetry was compared in the entire trial cohort between the patients who developed grade 2+ urinary toxicity and those who did not (Fig. 4B), only mean V5-15 Gy showed a small but statistically significant difference. On symptom-wise analysis, bladder mean dose was significantly higher for patients with dysuria (V5-V35 Gy), urgency (V5-V15 Gy), frequency and incontinence (V5 Gy), but not for hematuria and urinary obstruction (Fig. E1A-F). No significant difference was observed over higher dose range for any of the urinary symptoms.

Multivariable analysis (Table 2) for cumulative grade 2+ urinary toxicity included bladder dosimetric variables with the mean V10 and V40 Gy to represent low (5-15 Gy) and moderate (35-45 Gy) dose, respectively, which can be modulated reasonably independent of each other during

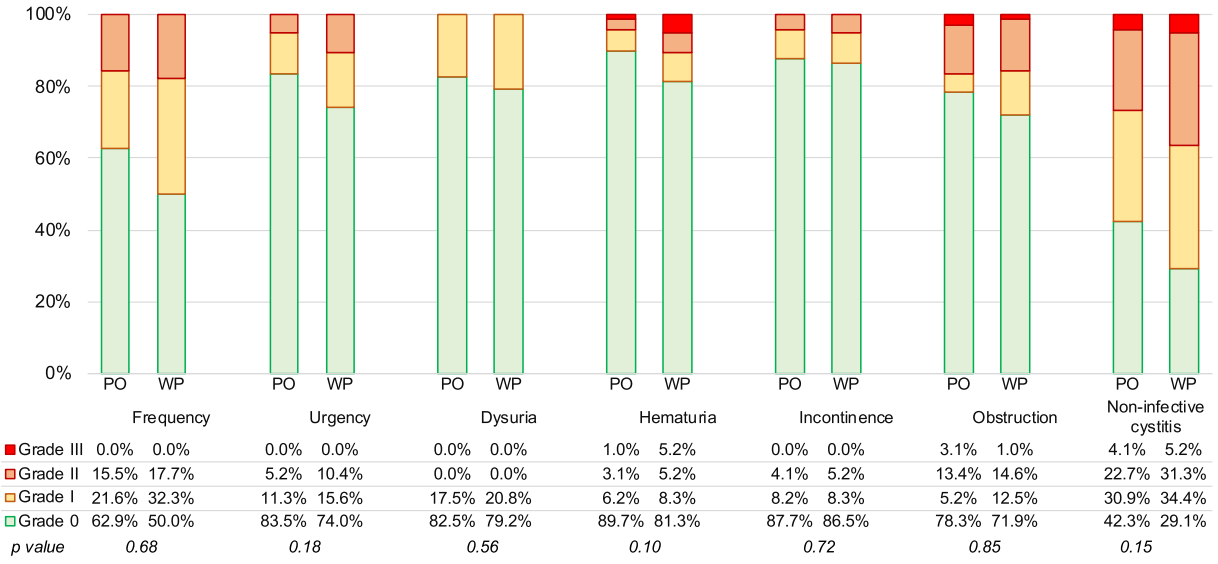


Fig. 2. Cumulative late Common Terminology Criteria for Adverse Events urinary toxicity symptoms in trial arms. *Abbreviations*: PO = prostate-only radiation therapy; WP = whole pelvic radiation therapy.

radiation therapy planning. No significant effect of the trial arm, bladder dose, or any of the other potential factors on cumulative late urinary toxicity was identified.

Discussion

Updated assessment of late urinary toxicity during long-term follow-up within the POP-RT trial affirms the safety of IG-IMRT based WPRT. Cumulative rate of severe urinary adverse effects remained low and was similar between the trial arms. Incidence of cumulative grade 2 toxicity in the WPRT arm continued to be about 10% higher than PORT, although not statistically significant. CTCAE-defined urinary symptoms as well as updated patient-reported QOL scores were similar between WPRT and PORT. Expectedly, the planned dose to the bladder was higher with WPRT, but bladder dosimetry showed no independent association with late urinary toxicity.

Post radiotherapy late urinary symptoms have been attributed to factors such as baseline urinary function, older age, diabetes mellitus, prior history of TURP, and acute urinary adverse effects.[7-9] However, none of these factors were independently associated with late urinary toxicity in the present study. Most prospective trials in the era of dose-escalated prostate IMRT emphasize the importance of high doses or hotspots to small volumes of bladder, especially the bladder neck and trigone.[10-12] Being a randomized trial, no difference in the higher doses to the bladder neck and trigone regions is expected between the PORT and WPRT arms. Despite the higher prostate dose (biologically effective dose, 129.6 Gy) and hypofractionation, the severe late urinary toxicity was similar (5%) to that in the RTOG 9413 trial where a conventionally fractionated lower dose (biologically effective dose, 112.3 Gy) and 3-dimensional conformal technique was used.[13]

Contribution of lower to mid range doses to the bladder, as expected in whole pelvic radiation therapy, has been uncertain. The POP-RT trial used constraints adapted from prostate IMRT trials of the time. Traditionally, irradiation of pelvic nodes to 40 to 50 Gy with 4-field box or 3-dimensional conformal technique used a full bladder to displace the small bowel out of irradiation field, with bladder dome receiving nearly the full nodal prescription dose. IMRT can reduce this dose, but to our knowledge no validated bladder dose constraints have been defined for 10 to 40 Gy. Although the planned bladder dose was comfortably below the protocol-specified constraints, larger volume of bladder did receive 5 to 50 Gy with pelvic radiation therapy, possibly contributing to slight increase in urinary symptoms. Although not reaching statistical significance, it may be worthwhile exploring the effect of these midlevel doses in future pelvic IMRT and proton therapy trials.

Reporting of radiotherapy related late toxicity in clinical trials of prostate cancer has not always been uniform. Urinary symptoms during follow-up may range from persistent frequency or urgency, which impairs daily activities, transient urethral stricture resolved after instrumental dilatation, or a combination of these. A composite score such as RTOG system may not capture detailed symptom severity as the CTCAE scale does, which identifies more grade 1 to 2 adverse effects.[14,15] In general, CTCAE grade 2 symptoms are medically manageable on an outpatient basis without requiring invasive interventions. None of these symptoms were observed to be significantly increased with pelvic radiation therapy on long-term follow-up in the present

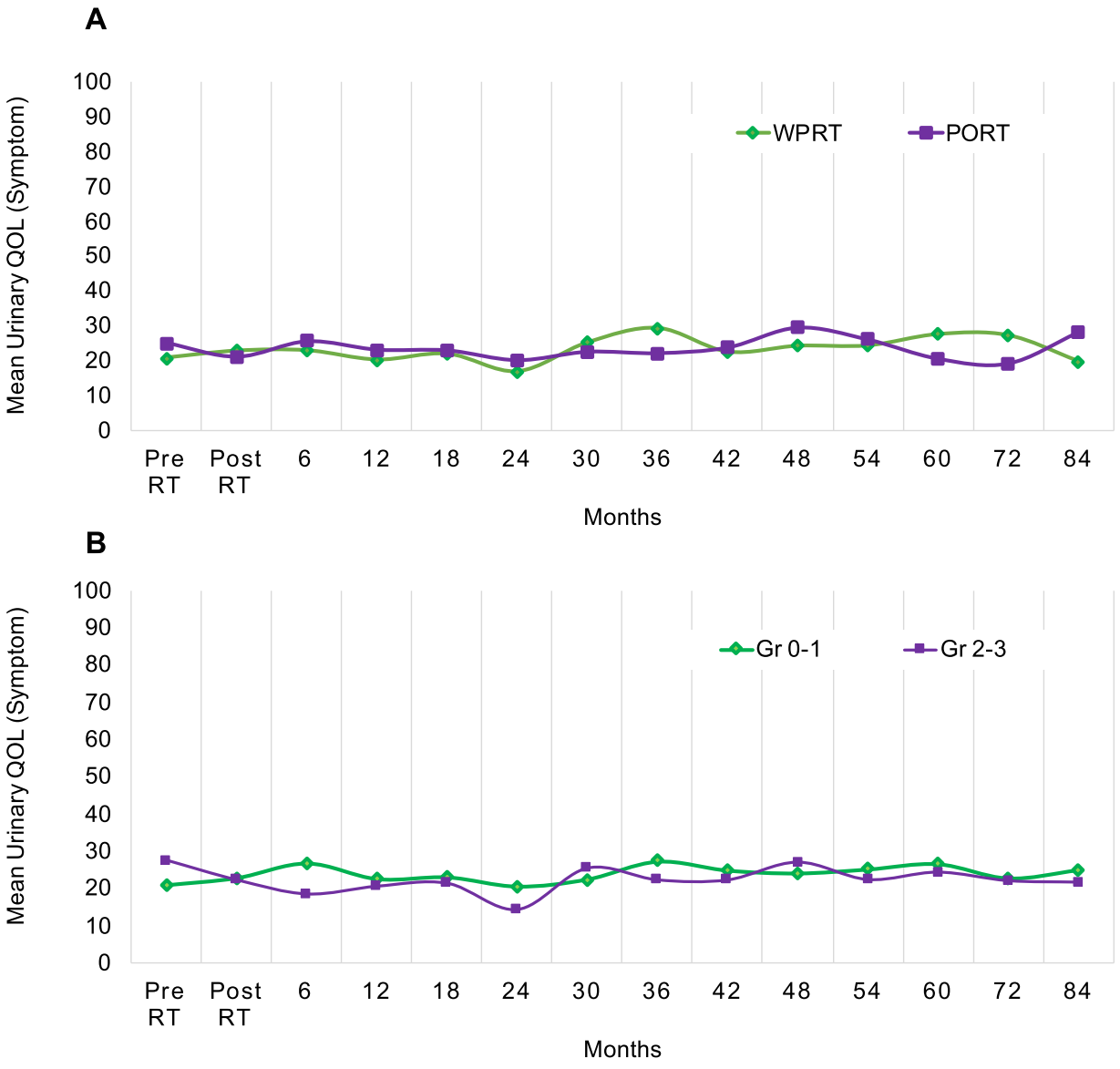
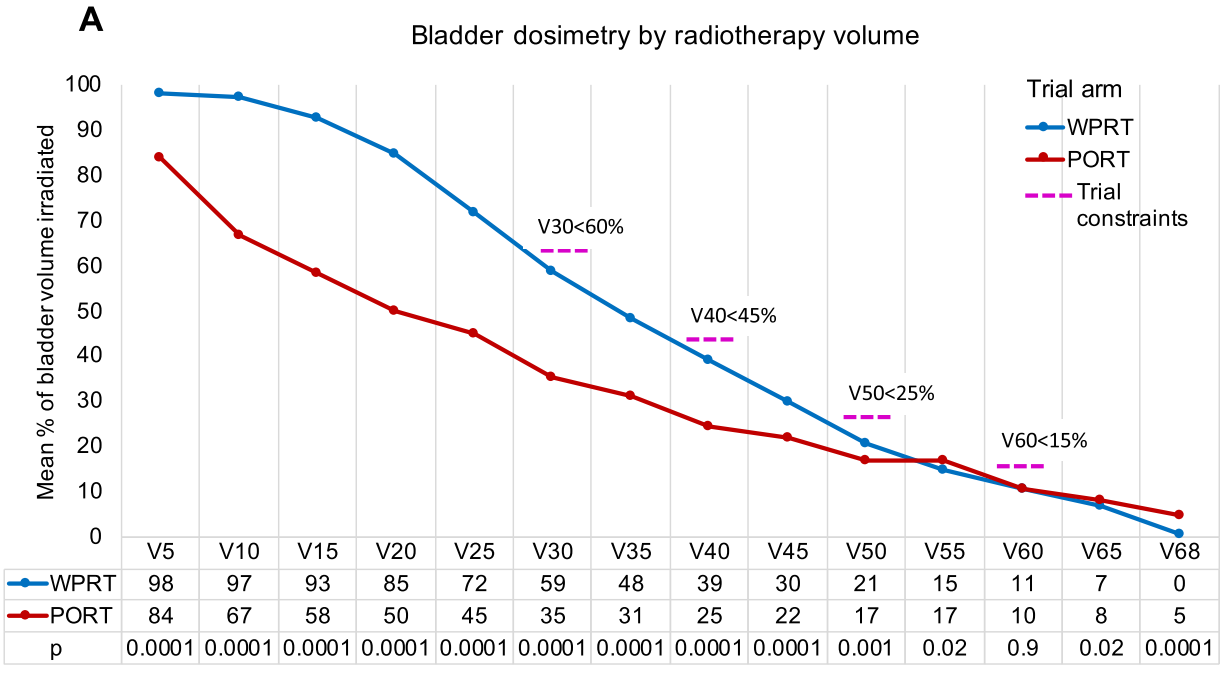


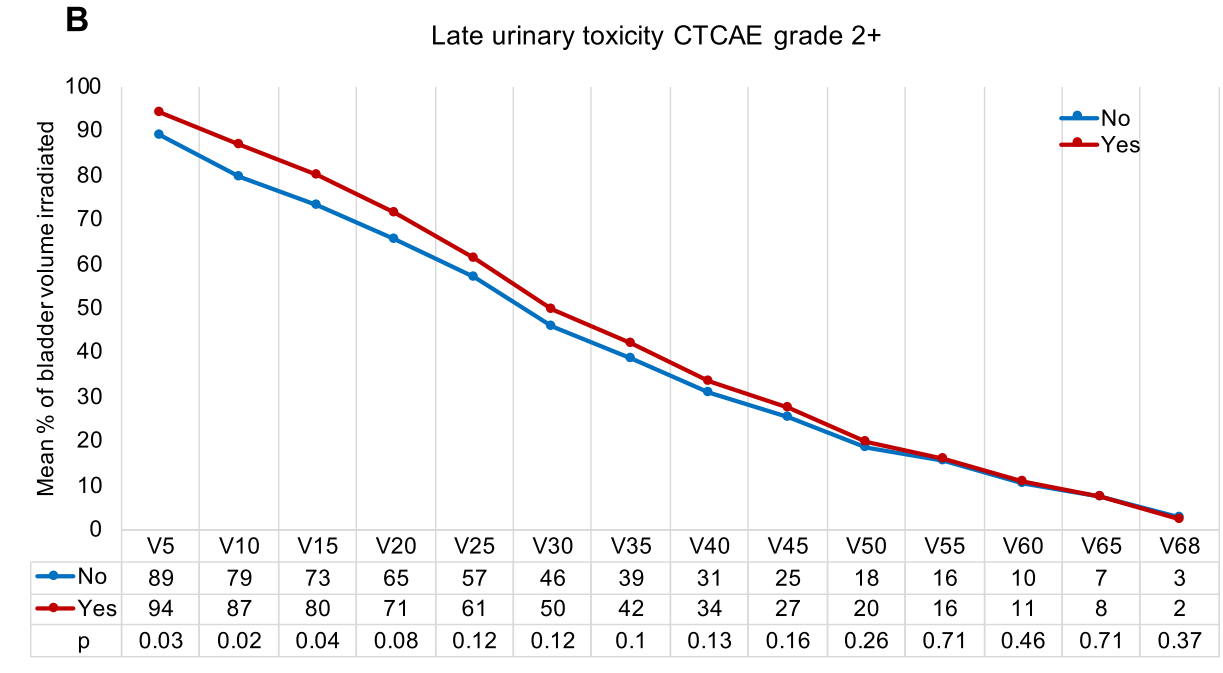
Fig. 3. Mean urinary quality of life (PR-25) scores compared for trial arms (A) and physician-reported late Common Terminology Criteria for Adverse Events urinary toxicity (B). *Abbreviations:* PORT = prostate-only radiation therapy; QOL = quality of life; RT = radiation therapy; WPRT = whole-pelvic radiation therapy.

analysis. Patient-reported QOL scores corroborate the acceptability of pelvic radiation therapy, showing no relevant difference between the trial arms. Serial QOL was not worse (≥10 points) at any time point for patients with physician-assessed grade 2 to 3 toxicities, indicating the transient and manageable nature of symptoms. Considering the large benefit in disease control, and consequent reduction in need for salvage treatment, omitting pelvic radiation routinely is not justified for most patients with locally advanced high-risk prostate cancer.

The present study explored plausible contributory factors for late urinary toxicity after WPRT, identifying no significant effect of target volume or bladder dosimetry. Nearly 30% patients in this study had a TURP before radiation , likely higher than the global West but in line with clinical practice in India.[16] Prior TURP was a stratification factor at randomization in the trial, and no independent association of TURP with late urinary toxicity was observed in this study. As a limitation, this analysis does not include doses to bladder subregions, which may affect various urinary symptoms differently. Urethral injury could also contribute to urinary symptoms such as obstruction but could not be addressed in this study due to the homogenous dose distribution within the prostate PTV for all patients. Accumulated dose to the bladder, the actual sum of the dose



	V5	V10	V15	V20	V25	V30	V35	V40	V45	V50	V55	V60	V65	V68
WPRT	98	97	93	85	72	59	48	39	30	21	15	11	7	0
PORT	84	67	58	50	45	35	31	25	22	17	17	10	8	5
p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.001	0.02	0.9	0.02	0.0001



	V5	V10	V15	V20	V25	V30	V35	V40	V45	V50	V55	V60	V65	V68
No	89	79	73	65	57	46	39	31	25	18	16	10	7	3
Yes	94	87	80	71	61	50	42	34	27	20	16	11	8	2
p	0.03	0.02	0.04	0.08	0.12	0.12	0.1	0.13	0.16	0.26	0.71	0.46	0.71	0.37

Fig. 4. Bladder dosimetry compared for radiation therapy volume (A) and late Common Terminology Criteria for Adverse Events urinary toxicity (B). *Abbreviations:* PORT = prostate-only radiation therapy; WPRT = whole-pelvic radiation therapy.

delivered during each fraction, may differ from planned dose, and may contribute to unforeseen toxicity. These will be explored in future studies. There may be scope to reduce urinary toxicity further by even stricter constraints, especially in the 10 to 40 Gy range. With this data from the POP-RT trial providing a benchmark, outcomes of ongoing large randomized trials such as RTOG 0924 (NCT01368588), Prostate Radiotherapy in High-Risk and Node-Positive Disease Comparing Moderate and Extreme Hypofractionation (NCT03561961), and Prostate and Pelvic Lymph Node Versus Prostate only Radiotherapy With or Without Prostate Boost in Advanced Localised Prostate Cancer (ISRCTN80146950) are awaited to refine the practice of IMRT-based pelvic radiotherapy.[17-19]

Table 2 Multivariable analysis for cumulative grade 2+ late urinary toxicity

		Univariable analysis		Multivariable analysis	
Variable	**Grouping**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age	Continuous	0.98 (0.94-1.02)	.32	0.98 (0.94-1.02)	.31
T stage	<T3b	Ref	.56	Ref	.77
	>T3b	1.20 (0.65-2.20)		1.21 (0.54-2.69)	
Diabetes	No	Ref	.11	Ref	.15
	Yes	1.71 (0.88-3.32)		1.68 (0.84-3.34)	
TURP	No	Ref	.34	Ref	.32
	Yes	1.38 (0.69-2.75)		0.71 (0.35-1.45)	
Trial arm	PORT	Ref	.15	Ref	.77
	WPRT	1.57 (0.85-2.89)		1.22 (0.52-2.84)	
Grade 2+ acute urinary toxicity	No	Ref	.11	Ref	.09
	Yes	1.76 (0.86-3.50)		1.85 (0.91-3.77)	
Bladder V10 Gy	Continuous	1.01 (1.00-1.03)	.04	1.02 (0.99-1.05)	.13
Bladder V40 Gy	Continuous	1.02 (0.99-1.04)	.15	0.98 (0.93-1.03)	.40

Abbreviations: HR = hazard ratio; PORT = prostate-only radiation therapy; TURP = transurethral resection of prostate; WPRT = whole pelvic radiation therapy.

Conclusion

During long-term follow-up, whole pelvic radiotherapy resulted in low (∼5%) and similar grade 3 cumulative urinary toxicity as prostate-only radiotherapy. Long-term patient-reported QOL scores were similar, and no causative factors affecting the late urinary toxicity were identified.

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