

High-Grade Late Urinary Toxicity Following Salvage Radiotherapy After Radical Prostatectomy: A Retrospective Cohort Study

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Purpose: To find out the incidence and predictors for late high-grade genitourinary (GU) toxicity following salvage radiotherapy (SRT), we investigated the consecutive patients who were treated with SRT after radical prostatectomy.

Materials and Methods: Patients who underwent SRT for biochemical recurrence after radical prostatectomy were reviewed. The incidence of GU toxicity was assessed and risk factors for grade ≥ 2 and ≥ 3 GU toxicity were evaluated. The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guided the reporting of this study.

Results: Among the total of 217 patients, 88 patients (40.5%) showed late grade ≥ 2 GU toxicity. The incidence of late grade ≥ 3 GU toxicity was 11.5%. The presence of grade ≥ 2 baseline GU dysfunction (hazard ratio [HR], 6.097; 95% confidence interval [CI], 3.280–11.333; $p < 0.001$) and short interval (< 1 year) from surgery to SRT (HR, 1.994; 95% CI, 1.182–3.365; $p = 0.01$) were associated with late grade ≥ 2 GU toxicity. A short interval from surgery to SRT was an independent predictor of late grade ≥ 3 GU toxicity (HR, 2.975; 95% CI, 1.135–7.794; $p = 0.027$).

Conclusions: The incidence of late high-grade GU toxicity was not uncommon after SRT. Thus, care should be taken when we consider SRT in patients with baseline urinary dysfunction and a short interval from surgery to SRT, to determine an optimal treatment strategy with balancing quality of life and oncologic outcome of patients.

Key Words: Prostatic neoplasms, Radical prostatectomy, Salvage radiotherapy, Urinary toxicity

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INTRODUCTION

Salvage radiotherapy (SRT) is the potentially curative

treatment option for patients with prostate-specific antigen (PSA) recurrence after radical prostatectomy (RP) but no evidence of distant metastatic disease, through the eradication

of microscopic residual disease [1,2]. SRT after RP is applied to the prostatic bed and possibly to the surrounding tissues, including lymph nodes [3]. Regarding survival outcomes of SRT in postprostatectomy patients, we previously reported that SRT with or without subsequent androgen deprivation therapy (ADT) demonstrated better clinical progression-free survival compared to ADT only [4]. Several studies of SRT demonstrated that 5-year biochemical progression-free survival outcomes following SRT ranged from 40% to 90% and better results are achieved with a lower PSA at initiation of SRT [5-12]. However, SRT could result in an increasing risk of morbidity in relation to acute and late toxicity following irradiation [6,8]. Genitourinary (GU) toxicity plays a major role in the post-treatment quality of life in patients who have undergone SRT, because SRT could aggravate the RP complications such as urinary incontinence or urethral stricture [8,13,14]. In the current study, we investigated the acute and late GU toxicity of patients, and evaluated the pre-SRT clinical factors which predict late grade ≥ 2 and ≥ 3 GU toxicity not only to aid selecting patients who would benefit more from SRT but also to determine an optimal treatment strategy before SRT.

MATERIALS AND METHODS

The STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) guidelines were followed to conduct this retrospective cohort study. After obtaining approval from the Institutional Review Board of University of Ulsan College of Medicine, Asan Medical Center (No. 2017-1036), the medical records of prostate cancer patients who underwent SRT with a curative intent for biochemical recurrence (defined as 2 consecutive postoperative PSA values ≥ 0.2 ng/mL) after a period of undetectable PSA or persistent postoperative PSA between 1998 and 2015 at University of Ulsan College of Medicine, Asan Medical Center, were reviewed. Patients with incomplete data or short follow-up periods of less than 1 year were excluded from the analysis. Finally, a total of 217 patients were evaluated in this study. Our institutional protocol of SRT was described in our previous report [4]. Briefly, computed tomography simulation was performed before SRT. External beam radiotherapy (RT) was delivered for SRT, including either

the whole pelvis or prostate bed according to the Roach score [15]. Patients with a Roach score $\geq 15\%$ received whole-pelvis RT, whereas the others received prostate bed RT. After 45–50 Gy of whole-pelvis RT, a reduced field boost, up to a mean of 66.5 Gy, was delivered in patient treated with whole-pelvis RT. Sixty-five patients (30.0%) were treated with 3-dimensional conformal RT (3D-CRT) using four-field box technique. The remaining 152 patients (70.0%) were treated according to intensity-modulated RT (IMRT) schemes using 5 to 7 fields which were created using Eclipse 10.0 (Varian Medical Systems, Palo Alto, CA, USA). The planning target volume was a 5- to 7-mm expansion of the clinical target volume. A median (range) dose of 66.0 Gy (47.8–77.0 Gy) with a daily fraction size of 1.8–2.0 Gy was delivered with a 15-MV x-ray from a linear accelerator (Clinac 1800, 2100 C/D, Varian Medical System).

Patients had follow-up visits every 3 to 6 months after SRT up to 3 years, and then annually thereafter. Acute toxicities were those occurring during treatment or within 3 months after treatment. Late toxicities were those occurring after 3 months of treatment or those that started acutely and lasted for 3 months after treatment. Acute and late gastrointestinal (GI) and GU toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. The CTCAE displays grades 1 through 5 with clinical descriptions of severity for each adverse event. Briefly, grade 2 is defined as moderate adverse event (minimal, local or noninvasive intervention indicated), and grade 3 is defined as severe or medically significant but not immediately life-threatening adverse event (hospitalization or prolongation of hospitalization indicated, limiting self-care activities of daily living). Because we assumed that a substantial proportion of patients had urinary dysfunction such as frequency, urgency, or urinary incontinence following RP, baseline GU dysfunction was assessed for every patient before SRT and it was graded according to the same criteria as toxicity grading.

Kaplan-Meier analyses were used to determine the 5-year risk of late grade ≥ 2 and ≥ 3 GU toxicity. To identify the predictive factors for the high-grade late GU toxicity, the following factors were analyzed: age, body mass index, presence or absence of hypertension and diabetes, time interval from RP to SRT, whether patients were taking ADT or not, RT modality, RT dose, RT field, year of RT, and

baseline GU dysfunction. Univariable and multivariable Cox regression models were used for predictive analysis. SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses; $p < 0.05$ was considered statistically significant.

RESULTS

The baseline and treatment characteristics of the 217 patients are summarized in Table 1. The median age was 64 years. The median time interval from RP to SRT was 22.7 months. ADT was administered in 97 patients (44.7%). Most patients (70.0%) were treated with IMRT, while the remaining 30.0% of patients were treated with 3D-CRT.

Table 1. Clinical characteristics of 217 patients who underwent salvage radiotherapy after radical prostatectomy

Characteristic	Value
Age (yr)	64 (59–68)
Preoperative PSA (ng/mL)	13.8 (7.7–27.1)
<10	81 (37.3)
10–20	61 (28.1)
≥20	75 (34.6)
Pathologic Gleason score	
≤6	9 (4.2)
7	99 (46.7)
8–10	104 (49.1)
Extracapsular extension	83 (38.2)
Seminal vesicle invasion	65 (30.0)
Positive surgical margins	131 (60.4)
PSA before radiotherapy (ng/mL)	0.66 (0.39–1.0)
<0.5	74 (34.1)
0.5–1.0	91 (41.9)
≥1.0	52 (24.0)
Time from RP to RT (mo)	22.7 (11.8–39.8)
<12	57 (26.3)
12–24	57 (26.3)
≥24	103 (47.4)
ADT	97 (44.7)
Radiotherapy modality	
3D-CRT	65 (30.0)
IMRT	152 (70.0)
Radiotherapy dose (Gy)	66.0 (66.0–70.0)
Radiation fields	
Prostatectomy bed	66 (30.4)
Whole pelvis	151 (69.6)
Year of radiotherapy	
1998–2008	56 (25.8)
2009–2010	72 (33.2)
2011–2013	89 (41.0)

Values are presented as median (interquartile range) or number (%).

PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy; ADT, androgen deprivation therapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

The median RT dose was 66.0 Gy and most patients (86.6%) were treated with total dose of ≥ 66 Gy. Whole-pelvis RT was performed in 151 patients (69.6%).

Forty-eight patients (22.1%) had acute grade ≥ 2 GU toxicity. The frequency (66.0%) was the most common acute grade 2 GU toxicity followed by urinary incontinence (22.6%). Four patients had acute grade 3 GU toxicity with urethral stricture, ureteral stricture, and urinary incontinence.

The overall incidence of late grade ≥ 2 GU toxicity was 40.5%. Urinary incontinence (57.7%) was most common late grade 2 GU toxicity followed by hematuria (22.5%). Although these patients were treated with medication, their symptoms waxed and waned over the years. Twenty-five patients (11.5%) had late grade 3 GU toxicity. Hematuria (56%) was the most common late grade 3 GU toxicity followed by urinary incontinence (36%). No grade 4 or higher acute and late GU toxicities were reported (Table 2). The 5-year risk of late grade ≥ 2 GU toxicity was 43.0% and that of late grade 3 GU toxicity was 11.6% (Fig. 1). The median time to development of first late grade ≥ 2 and grade 3 GU toxicity was 20.3 (interquartile range [IQR], 11.1–31.5) and 28.7 (IQR, 22.6–48.4) months, respectively.

A total of 57 patients received SRT within 1 year after RP. Among them, 36 (63.2%) and 14 patients (24.6%) developed late grade ≥ 2 and grade 3 GU toxicity, demonstrating a high risk of late GU toxicity, compared to patients who had received SRT ≥ 1 year after RP (late grade ≥ 2 toxicity; 32.5%, grade 3 GU toxicity; 6.9%).

Of the 22 patients with a baseline grade ≥ 2 GU dysfunction, 18 (81.8%) and 6 patients (27.3%) developed late grade ≥ 2 and grade 3 GU toxicity, while 35.9% and 9.7% of patients with a baseline grade ≤ 1 GU dysfunction developed late grade ≥ 2 and grade 3 GU toxicity, respectively. A similar trend was observed with respect to urinary incontinence. Of

Table 2. The incidence of acute and late toxicity after salvage radiotherapy (n=217)

Grade of toxicity	Baseline GU dysfunction	Incidence of acute GU toxicity	Incidence of late GU toxicity
0	167 (76.9)	99 (45.6)	75 (34.6)
1	28 (12.9)	70 (32.3)	54 (24.9)
2	21 (9.7)	44 (20.3)	63 (29.0)
3	1 (0.5)	4 (1.8)	25 (11.5)

Values are presented as number (%).

GU, genitourinary.

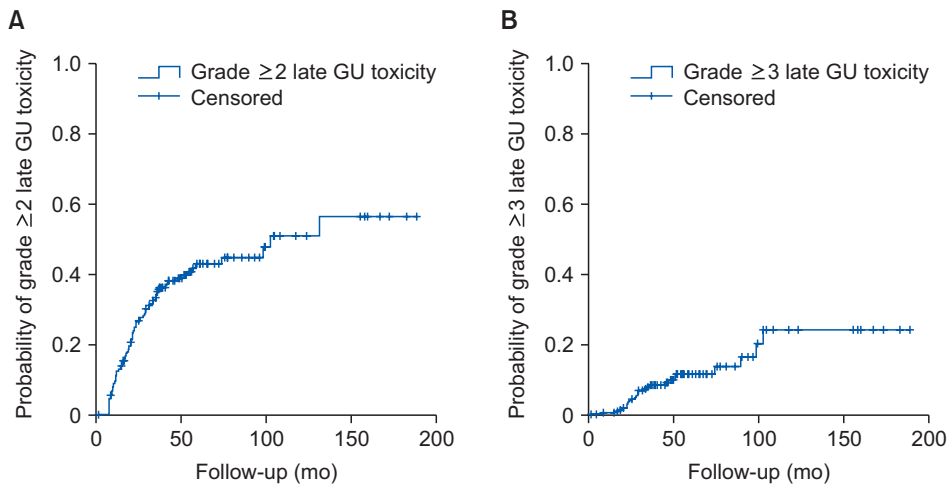


Fig. 1. Risk of 5-year late (A) grade ≥ 2 and (B) grade 3 urinary toxicity. GU, genitourinary.

the 15 patients with baseline grade ≥ 2 urinary incontinence, 9 (60%) and 3 patients (20%) reported late grade ≥ 2 and grade 3 urinary incontinence, while 17.8% and 3.0% of patients with baseline grade 0–1 urinary incontinence reported late grade ≥ 2 and grade 3 urinary incontinence, respectively.

Multivariable analysis demonstrated that a short time interval (<1 year) from RP to SRT (hazard ratio [HR], 1.994; 95% confidence interval [CI], 1.182–3.365; $p=0.01$) and baseline grade ≥ 2 GU dysfunction (HR, 6.097; 95% CI, 3.280–11.333; $p<0.001$) were independent predictive factors for late grade ≥ 2 GU toxicity. A short time interval from RP to SRT was an also independent predictive factor for late grade ≥ 3 GU toxicity (HR, 2.975; 95% CI, 1.135–7.794; $p=0.027$). Although it was not statistically significant, baseline grade ≥ 2 GU dysfunction showed a trend toward increasing risk of late grade ≥ 3 GU toxicity (HR, 2.500; 95% CI, 0.905–6.904; $p=0.077$) (Table 3).

With respect to GI toxicity, acute grade ≥ 2 GI toxicity was reported in 34 patients (15.7%). Most of acute grade 2 GI toxicity was diarrhea (40.0%). One patient had acute grade 3 GI toxicity with rectal hemorrhage. The overall incidence of late grade ≥ 2 GI toxicity was 6.9%. Most of late grade 2 GI toxicity was proctitis (58.3%). Three patients had late grade 3 GI toxicity including rectal hemorrhage and proctitis. No grade ≥ 4 GI toxicity was reported (Table 2). The 5-year risk of late grade ≥ 2 GI toxicity was 7.9% and that of late grade 3 GI toxicity was 2.1%.

DISCUSSION

Previous studies have demonstrated the low incidence of GI and GU toxicity following SRT after RP reporting serious late toxicity rates of 10% or less and suggested that SRT appears to be well-tolerated in patients [5,6,13,14,16,17]. In daily clinical practice, however, it is not uncommon that we face patients who complain of late urinary toxicity after SRT. Cozzarini et al. [18] reported higher than expected severe late urinary toxicity after hypofractionated adjuvant RT (ART) or SRT demonstrating 18% of a 5-year risk of late grade ≥ 3 urinary toxicity. Van Dessel et al. [8] reported late grade ≥ 2 toxicity for GU was 29.9% after SRT in accordance with our results. These results might be affected by hypofractionation, radiation dose, and the potential bias linked to the more vigilant attitude toward urinary toxicity in patients treated more recently. However, patients' quality of life is as important as survival outcomes and treatment related toxicity is an important factor for planning treatment strategy for patients [3]. In that sense, a vigilant attitude toward the toxicity of patients is required to clinicians in daily practice. In the current study, we reviewed acute and late toxicity of patients after SRT in detail. Furthermore, we investigated predictive factors of grade ≥ 2 and ≥ 3 late GU toxicity not only for better selection of patients before SRT, but also for better decision making regarding the timing of SRT, along with balancing the oncologic outcome and safety of patients.

According to prior studies assessed GI and GU toxicity after SRT, the incidence of acute grade ≥ 2 GI and GU toxicity

Table 3. Predictive factors for late grade ≥ 2 or grade 3 GU toxicity

Variable	Late grade ≥ 2 GU toxicity			Late grade 3 GU toxicity		
	Univariate	Multivariate		Univariate	Multivariate	
	p-value	HR (95% CI)	p-value	p-value	HR (95% CI)	p-value
Age (yr)	0.035	1.029 (0.991–1.067)	0.133	0.311	1.021 (0.957–1.089)	0.527
BMI (kg/m ²)	0.317	0.988 (0.905–1.079)	0.792	0.522	1.039 (0.879–1.228)	0.651
HTN	0.334	1.265 (0.782–2.045)	0.338	0.938	1.200 (0.486–2.964)	0.692
DM	0.833	1.237 (0.687–2.225)	0.479	0.519	0.656 (0.175–2.463)	0.532
Time from RP to SRT (mo)						
≥ 24	Reference			Reference		
12–24	0.389	1.559 (0.870–2.792)	0.135	0.980	1.013 (0.367–3.843)	0.985
<12	<0.001	1.994 (1.182–3.365)	0.010	0.005	2.975 (1.135–7.794)	0.027
ADT	0.072	0.670 (0.421–1.068)	0.092	0.748	1.028 (0.428–2.469)	0.950
Radiotherapy modality						
3D-CRT	Reference			Reference		
IMRT	0.593	0.374 (0.135–1.037)	0.059	0.786	0.988 (0.245–3.983)	0.986
Radiotherapy dose (Gy)						
≤ 66	Reference			Reference		
>66	0.807	1.106 (0.639–1.912)	0.719	0.435	1.570 (0.587–4.201)	0.369
Radiation field						
Prostatectomy bed	Reference			Reference		
Whole pelvis	0.440	0.712 (0.399–1.270)	0.250	0.786	1.883 (0.577–6.142)	0.294
Year of radiotherapy						
1998–2008	Reference			Reference		
2009–2010	0.280	1.240 (0.648–2.372)	0.516	0.414	1.241 (0.331–4.652)	0.749
2011–2012	0.169	1.786 (0.798–3.995)	0.158	0.284	2.875 (0.610–13.548)	0.182
Baseline GU dysfunction						
Grade 0–1	Reference			Reference		
Grade ≥ 2	<0.001	6.097 (3.280–11.333)	<0.001	0.004	2.500 (0.905–6.904)	0.077

GU, genitourinary; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HTN, hypertension; DM, diabetes; RP, radical prostatectomy; SRT, salvage radiotherapy; ADT, androgen deprivation therapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

was reported by 10%–18% and 9%–20%, respectively [5,6,11–14,18]. The incidence of acute grade 3 GI and GU toxicity was less than 5% in these studies. Although the incidence of acute grade ≥ 2 GU toxicity (22.1%) was slightly higher in the current study, our findings with respect to the incidence of acute toxicity were in accordance with prior studies.

The 5-year risk of late grade ≥ 2 and grade 3 GI toxicity (7.9% and 2.1%) was similar to previous reports ($\leq 10\%$ and $\leq 5\%$) [5,6,14,16,17,19]. However, the overall incidence and 5-year risk of late grade ≥ 2 and grade 3 GU toxicity of the current study was higher than other published reports (grade ≥ 2 ; 10%–30%, grade ≥ 3 ; 1%–10%) [5,6,12,13,16–19]. Possible explanations for this discrepancy are retrospective character of some series, and different materials and methods of those studies including statistical analysis, SRT protocol, and toxicity grading system.

In our study, short time interval (< 1 year) from RP to SRT was associated with late high-grade (grade ≥ 2 or ≥ 3)

GU toxicity. Time interval from RP to SRT was not clearly demonstrated for a predictive factor, or not associated with late high-grade GU toxicity in several prior studies [5,6,13,17,18]. However, these results should be interpreted carefully, because predictive analyses were not clearly demonstrated and several possible confounding factors were not adjusted in their studies. In addition, a small number of patients with a short time interval (< 1 year) from RP to SRT in those studies might be the possible reason for their inconsistent results. We evaluated as many as possible confounding variables based on published reports assessed toxicity after SRT, and patients with incomplete data were excluded from the analysis. The median time interval from RP to SRT of the current study (22.7 months) was short, compared with other studies (29–36 months) [5,6,13]. This might be the reason for our high risk of late grade ≥ 2 and grade 3 GU toxicity. Moreover, results of the recent 3 randomized controlled trials (GETUG, RADICALS, RAVES)

that compare the efficacy and safety of ART versus SRT support our findings [11,12,20]. All these trials demonstrated that SRT results in similar biochemical control to ART, and is associated with significantly lower amounts of GU toxicity. One of these studies concluded that observation with salvage treatment for PSA biochemical progression should be the current standard of care after RP [20]. Thus, we can assume that short time interval from RP to RT increased the risk of high-grade GU toxicity, and a longer time interval between RP and RT might lower the risk of toxicity.

CTCAE is a well-defined and standardized grading scale system that can be utilized for adverse event reporting. However, it seems that grading of toxicity is rather subjective, because adverse events are usually determined and graded by clinicians largely based on their beliefs and practices. In that sense, the perspective of radiation oncologists and urologists may be different. Several studies confirmed different practice patterns between radiation oncologists and urologists [21,22]. In our study, urologists tended to prescribe medication (CTCAE grade 2) for patients who complained of urinary symptoms, while radiation oncologists did not (CTCAE grade 1) do the same for the same patients (data not shown). Indeed, almost all prior studies that assessed toxicity after SRT were written by radiation oncologists [5,6,13,16-18]. Further study would be needed to verify this tendency, but this might have affected our results.

Goenka et al. [5] demonstrated that baseline GU dysfunction grade ≥ 2 (HR; 2.7, $p=0.01$) was associated with increased late grade ≥ 2 GU toxicity after SRT. Furthermore, poor baseline urinary incontinence was associated with an increased risk of developing late grade ≥ 2 urinary incontinence (HR, 4.21; $p<0.01$). We confirmed these findings in the current study demonstrating an increased risk of late grade ≥ 2 GU toxicity in patients with a baseline grade ≥ 2 GU dysfunction (HR, 6.1; $p<0.001$). Although not significant, a baseline grade ≥ 2 GU dysfunction was associated with increased late grade 3 GU toxicity (HR, 2.5; $p=0.077$).

With respect to oncologic outcomes, early SRT at the low PSA level and higher SRT dose were associated with improvement in survival outcomes after SRT [7,9,11,12, 23,24]. Our findings would be helpful to determine the patient selection and timing of SRT maintaining the balance between oncologic outcome and toxicity. For instance, we

can consider ADT before SRT, and followed by high-dose SRT in patients with a baseline GU dysfunction and a short time since RP. Although the type and optimal duration of ADT in combination with SRT remains controversial, we can expect not only improved survival but also a reduced risk of late high-grade GU toxicity in these patients [11,25]. In our data, among the patients who showed biochemical recurrence within 1 year after RP, 35 patients received SRT ≥ 1 year after RP due to a period of ADT before SRT. The incidence of late grade ≥ 2 and grade 3 GU toxicity of these patients was lower than that of patients who received SRT <1 year after RP (late grade ≥ 2 toxicity, 25.7% vs. 63.2%; grade 3 GU toxicity, 2.9% vs. 24.6%). Furthermore, the 5-year biochemical progression-free survival rates following SRT were better in the former group than those of the latter group (57% vs. 33%). These findings support our suggestion regarding the patient selection and timing of SRT with a balancing between the oncologic outcome and toxicity.

Our study had several limitations including the potential bias inherent in retrospective studies. The patients who received ART were not analyzed in the current study. Therefore, our findings cannot be generalized to ART. However, recent 3 randomized controlled trials demonstrated that ART increases the risk of urinary morbidity with no benefit for biochemical control compared with SRT [11,12,20]. Our findings will provide additional information for the management strategy of patients in relation to toxicity after SRT.

CONCLUSIONS

Our results showed the high incidence of late high-grade GU toxicity after SRT. In addition, a baseline grade ≥ 2 GU dysfunction and a short time (<1 year) interval from surgery to SRT are associated with an increased risk of late high-grade GU toxicity. Therefore, more time for potential recovery from urinary dysfunction or an alternative treatment strategy should be provided to patients so that they can benefit more from SRT maintaining a balance between the oncologic outcome and treatment related toxicity.

NOTES

- **Author Contribution:** Conceptualization: HA; Data cura-

tion: SKC, SML; Formal analysis: SKC; Methodology: SKC, MK; Project administration: HA; Visualization: SKC; Writing - original draft: SKC; Writing - review & editing: SKC, MK, SML, CS, JHH, CSK.

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