Temporal Patterns and Resolution of Toxicities following Hypofractionated Salvage Radiotherapy for Biochemical Recurrence of Prostate Cancer After Prostatectomy

Abstract

Background: Hypofractionated salvage radiotherapy (RT) is increasingly used for biochemical recurrence of prostate cancer post-prostatectomy, yet its toxicity profile remains underexplored. This study evaluates the incidence, timing, and resolution of treatment-related toxicities in this setting.

Materials and Methods: A retrospective cohort study of 403 men receiving hypofractionated salvage RT (62.5 Gy in 25 fractions) from 2017–2024 was conducted. Toxicities, categorized as genitourinary (GU: hematuria, urinary incontinence, fre-quency, dysuria) or gastrointestinal (GI: rectal bleeding, diarrhea, proctitis, nausea), were graded (1–3) using CTCAE-based criteria. Outcomes included any-time incidence, Kaplan–Meier time-to-first-event estimates (12-/24-month cumulative incidence), and first-onset timing. Episode-level analyses merged events $\leq$30 days apart, assessing resolution and intervention.

Results: Median follow-up was 18.2 months. Any-grade GU and GI toxicities occurred in 34.2% and 24.6% of patients, respectively. Specifically, urinary incontinence (20.3%) and rectal bleeding (19.9%) were common. Most toxicities were low-grade; Grade $\geq$2 incidence was low (e.g., hematuria 4.7%, incontinence 6.0%). Time-to-onset varied: acute events ($<$3 months) were rare for hematuria (median 17.8 months) but common for frequency/dysuria. Resolution rates for Grade 2 events were high ($>$65%) with conservative management or medication, though Grade 3 events often required procedural intervention.

Conclusion: Hypofractionated salvage RT demonstrates a manageable toxicity profile. Distinct temporal patterns suggest the need for prolonged monitoring for hematuria compared to acute urinary symptoms.

*Equally contributed.

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1 Introduction

Hypofractionated salvage radiotherapy (RT) is increasingly utilized for patients with biochemical recurrence of prostate cancer following prostatectomy. While the oncologic efficacy is well-documented, the detailed toxicity profile—specifically the temporal patterns of onset and resolution—remains less characterized compared to conventional fractionation. This study aims to evaluate the incidence, timing, and resolution of genitourinary (GU) and gastrointestinal (GI) toxicities in this specific cohort.

2 Materials and Methods

A retrospective cohort study was conducted involving 403 men who received hypofractionated salvage RT (62.5 Gy in 25 fractions) between 2017 and 2024.

Toxicity Assessment: Toxicities were categorized into Genitourinary (GU) symptoms (hematuria, urinary incontinence, urinary frequency, dysuria) and Gastrointestinal (GI) symptoms (rectal bleeding, diarrhea, proctitis, nausea). Severity was graded (1–3) based on CTCAE criteria.

Statistical Analysis: Outcomes included any-time incidence, Kaplan–Meier estimates for time-to-first-event (calculating 12- and 24-month cumulative incidence), and analysis of first-onset timing. For episode-level analysis, events occurring within 30 days of each other were merged to assess resolution patterns and required interventions.

3 Results

3.1 Incidence and Timing of Toxicities

The median follow-up period was 18.2 months. Any-grade GU toxicities were observed in 34.2% of patients, while GI toxicities occurred in 24.6%.

Table 1 summarizes the incidence and timing of specific symptoms based on the analysis. Urinary incontinence (20.3%) and rectal bleeding (19.9%) were the most frequent any-grade toxicities. However, severe toxicities (Grade $\geq$2) were relatively infrequent.

Table 1: Incidence and Timing of Toxicities

	Ever-event Incidence (95% CI)		**Cum. Inc. at 24 Months**		**First Onset Timing**	
Symptom	**Any Grade**	**Grade $\geq$2**	**Any Grade**	**Grade $\geq$2**	**Median Mo. [IQR]**	**% in 12-24m**
Urinary Incontinence	20.3 [16.7, 24.5]	6.0 [4.0, 8.7]	26.4	8.8	6.1 [6.0, 17.9]	29.3
Hematuria	13.9 [10.9, 17.6]	4.7 [3.0, 7.2]	18.7	6.4	17.8 [13.8, 23.8]	53.6
Urinary Frequency	7.9 [5.7, 11.0]	0.7 [0.3, 2.2]	9.1	1.0	2.6 [1.4, 4.3]	10.3
Dysuria	4.2 [2.7, 6.7]	0.0 [0.0, 0.9]	4.9	0.0	2.4 [0.6, 6.2]	5.9
Rectal Bleeding	19.9 [16.2, 24.0]	3.0 [1.6, 5.1]	24.9	3.2	10.9 [5.7, 18.2]	25.0
Proctitis	5.0 [3.2, 7.5]	1.0 [0.3, 2.5]	4.6	1.4	10.7 [7.6, 17.1]	33.3
Diarrhea	5.2 [3.4, 7.8]	0.5 [0.1, 1.8]	5.3	0.5	3.3 [1.0, 13.2]	14.3
Nausea	2.7 [1.5, 4.8]	0.0 [0.0, 0.9]	2.8	0.0	0.8 [0.6, 2.6]	0.0

3.2 Temporal Dynamics

The temporal dynamics of these toxicities are visualized in Figure 1. Hematuria tended to have a delayed onset compared to urinary frequency and dysuria. Figure 2 provides a heatmap visualization of first-onset distributions.

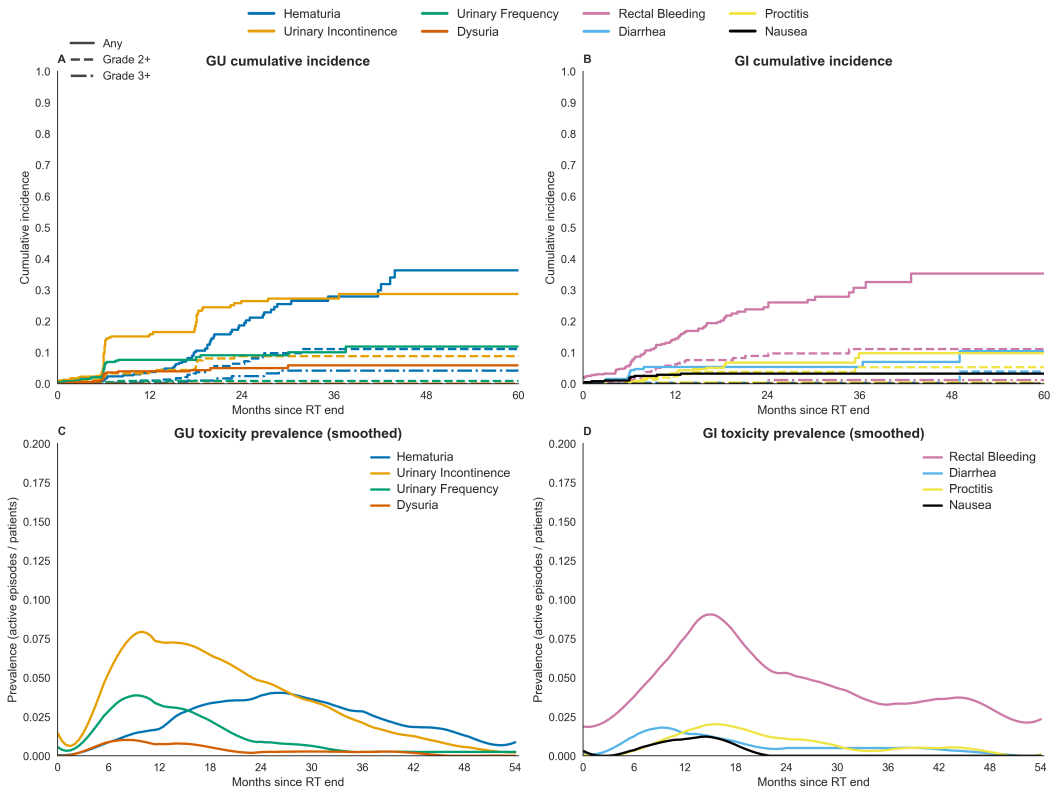

Figure 1: Time dynamics of toxicity onset. Kaplan-Meier curves showing cumulative incidence over time.

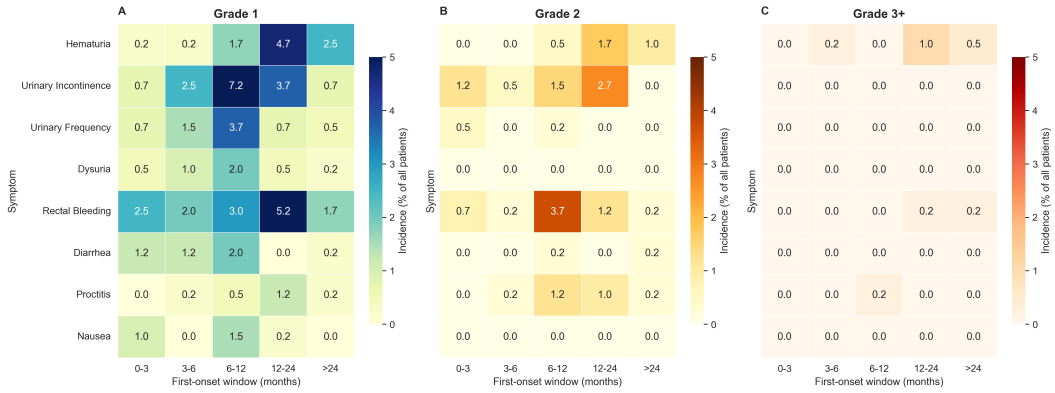

Figure 2: Heatmaps of first toxicity onset by symptom and grade over time.

3.3 Management and Resolution

We analyzed the management strategies and resolution outcomes for Grade 2 and Grade 3 toxicities (Table 2). For Grade 2 Hematuria, 69.2% of cases were managed supportively, while 30.8% required procedures.

Intervention types and the overall clinical course are depicted in Figures 3 and 4.

Table 2: Management and Outcomes for Grade 2 and Grade 3 Toxicities

Grade	Symptom	Supportive	Meds	Procedure	Surgery/Hosp.	Resolved (%)	Time to Res. [IQR]
Grade 2	Hematuria	69.2%	0.0%	30.8%	0.0%	69.2%	3.0 [2.0, 7.0]
	Urin. Incontinence	91.7%	8.3%	0.0%	0.0%	66.7%	5.0 [0.0, 12.2]
	Urin. Frequency	66.7%	33.3%	0.0%	0.0%	100.0%	6.3 [3.2, 6.8]
	Rectal Bleeding	38.5%	3.8%	57.7%	0.0%	69.2%	8.4 [4.5, 15.0]
	Proctitis	25.0%	25.0%	50.0%	0.0%	75.0%	8.1 [4.4, 12.2]
Grade 3	Hematuria	42.9%	0.0%	42.9%	14.3%	71.4%	3.6 [1.5, 12.3]
	Rectal Bleeding	0.0%	50.0%	0.0%	50.0%	50.0%	11.3 [N/A]

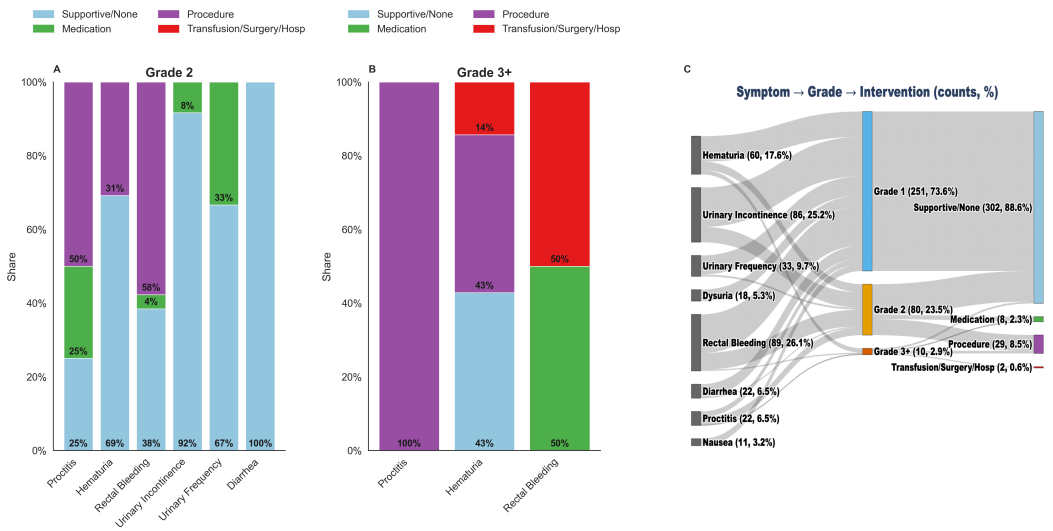

Figure 3: Distribution of interventions required for different toxicities.

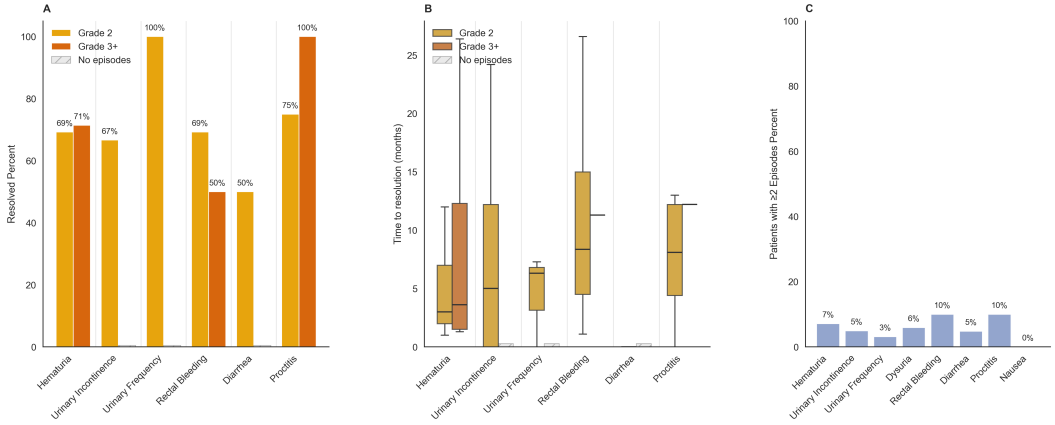

Figure 4: Clinical course and resolution status of toxicities.

4 Discussion

This study provides a comprehensive analysis of the toxicity profile associated with hypofractionated salvage RT. Our findings confirm that while low-grade toxicities are relatively common, high-grade events are rare. The temporal analysis reveals that while urinary frequency and dysuria are often acute and transient, hematuria and rectal bleeding may present with a delayed onset, necessitating long-term follow-up.

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