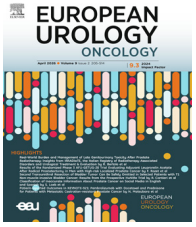
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Original Article

Real-World Burden and Management of Late Genitourinary Toxicity After Prostate Radiotherapy: Insights from IRRADIaTE, the Italian Registry of Radiotherapy-Associated Disorders and Urological Treatment & Evaluation

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Abstract

Background and objective: Radiotherapy (RT) is a key curative option for localized prostate cancer (PC). However, data on late genitourinary toxicity, especially adverse events requiring urgent care or hospitalization, remain limited. The aim of the Italian Registry of Radiotherapy-Associated Disorders and Urological Treatment & Evaluation (IRRADIaTE) is to characterize the burden and management of severe genitourinary adverse events following prostate RT across multiple high-volume centers in Italy.

Methods: A prospective, observational, multicenter registry was established in 2024 across 20 Italian institutions. Men with localized PC previously treated with curative, adjuvant, or salvage RT who presented with late (≥6 mo) genitourinary complications requiring urgent medical attention were enrolled. Demographics, treatment details, and outcomes were collected. Toxicity grading followed Common Terminology Criteria for Adverse Events. Primary endpoints were prespecified as (1) the cumulative incidence of grade 3–5 events with death as a competing risk and (2) hospitalization-free survival

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Complications

from RT completion. Analyses were descriptive and adjusted for prespecified confounders only.

Key findings and limitations: Among 321 patients, 50% received primary RT, and 50% postprostatectomy RT. At the time of admission, 43% presented with grade 3–5 genitourinary toxicity. Over 5 yr, the hospitalization-free survival rate declined from 86% to 42%. Higher cumulative incidence of severe events was observed in the primary RT group. The percentage of patients who did not require major surgery to manage RT-related complications decreased from 81% (95% confidence interval [CI] 76–97%) at 12 mo after RT to 66% (95% CI 48–79%) at 60 mo. Differences in baseline age and comorbidity profiles between the RT treatment settings must be acknowledged. Because the registry enrolls only men presenting with complications, population-level incidence and causal effects cannot be inferred.

Conclusions and clinical implications: Late genitourinary toxicity after prostate RT is substantial and often resource-intensive. Differences observed by treatment setting are associational; attribution of causal mechanisms and treatment effects requires dedicated causal-inference studies.

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ADVANCING PRACTICE

What does this study add?

This study provides the first prospective, national-level assessment of severe genitourinary toxicity following prostate cancer radiotherapy (RT) in Italy. The results highlight a substantial burden of late adverse events, and 43% of the patients admitted for RT-related genitourinary complications presented with grade 3–5 toxicity. Over 5 yr, the hospitalization-free survival rate declined from 86% to 42%. The proportion of patients who did not require major surgery for RT-related complications decreased from 81% (95% confidence interval [CI] 76–97%) at 12 mo to 66% (95% CI 48–79%) at 60 mo after RT. Notably, primary RT was associated with a greater cumulative risk of severe complications in comparison to adjuvant or salvage RT. These findings underscore the need to re-evaluate long-term toxicity in treatment planning and to promote integrated, multidisciplinary survivorship care.

Clinical Relevance

This large-scale registry study of over 300 patients highlights the real-world burden of late genitourinary toxicity after prostate radiotherapy. It provides novel insights into symptom trajectories, treatment patterns, and predictors of treatment failure, reinforcing the need for multidisciplinary collaboration and long-term follow-up in survivorship care. Editor-in-Chief: Morgan Rouprêt.

Patient Summary

This study looked at men who had radiotherapy for prostate cancer and later developed serious urinary problems. Many needed hospital care or even surgery, often years after their radiotherapy. Our results show that these long-term side effects are more common than expected and should be discussed with patients when they are choosing treatment.

1. Introduction

Most patients with prostate cancer (PC) are diagnosed with localized disease, for which treatment options include active surveillance, surgery, and radiotherapy (RT) [1]. Among these, RT is widely used; however, the long-term consequences, particularly the incidence and burden of late genitourinary toxicity, remain insufficiently characterized across different practice settings [2]. This knowledge gap is partly because of the late onset of RT sequelae and challenges in accurately recording such long-term adverse effects, as repeatedly noted in the literature [3]. Despite some investigations, multi-institutional data on the incidence and burden of genitourinary toxicity after RT remain scarce, which underscores the need for a better understanding to guide clinical practice and improve outcomes [4–9].

In this context, the IRRADIaTE registry (Italian Registry of Radiotherapy-Associated Disorders and Urological Treatment & Evaluation) is a national initiative designed to

enhance awareness among uro-oncologists and to address the need for systematic evaluation of these adverse events in routine clinical practice.

This IRRADIaTE registry study addressed a descriptive question: what is the burden and management of late genitourinary complications after prostate RT for patients presenting for urgent care? We also explored hypothesized causal pathways between initial treatment selection and toxicity outcomes within the limits of an observational framework.

2. Patients and methods

The study was designed as a prospective observational, nondrug, nondevice, multicenter national study and was conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Supplementary material) [10]. Ethical approval was first obtained from the lead institution (155CET, protocol no. 35988) and subsequently from all other participating centers.

The study period spanned from January 1 to December 31, 2024, with no restrictions on the date of prior RT.

Participating institutions were selected on a voluntary basis from the AGILE urological collaborative group. All were referral centers with urology and RT departments, as well as multidisciplinary teams, with established experience in PC treatment and adherence to current guideline-based indications [11].

All patients provided informed consent. The registry prospectively screened men with localized PC who had undergone RT with a curative, adjuvant, or salvage intent and who later experienced at least one late (occurring more than 6 mo after RT completion) genitourinary complication attributable to RT serious enough to require urgent evaluation (either via an emergency room or urgent outpatient consultation). Patients whose symptoms were deemed to be unrelated to RT after diagnostic work-up were excluded.

Investigators could reconstruct prior admissions related to RT-induced complications, which allowed longitudinal data capture. A dedicated analysis was reserved for patients requiring hospitalization or invasive management. The relationship between the event and RT was first assessed locally and was then centrally reviewed by the principal investigator. Patients with acute toxicity and those treated with brachytherapy or other non–external-beam RT (EBRT) modalities were excluded.

Demographic and medical history variables (including PC characteristics, comorbidities, prior treatments, symptoms, RT regimens, and radical prostatectomy [RP] technique) were prospectively collected. Each patient was followed for the period necessary to evaluate and manage the sequela according to standard clinical practice. Complications related to RT for PC were recorded in free text and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) scheme [12], with grades 3–5 considered severe or life-threatening.

2.1. Statistical analysis

Statistical analyses were performed using STATA version 17 (Stata Corporation, College Station, TX, USA) and followed established guidelines for reporting of statistics [13–15]. Results are summarized as the median and interquartile range (IQR) for continuous variables and as the frequency and proportion for categorical variables, and were compared using the Kruskal-Wallis test for continuous data, and Fisher's exact test or a χ^2 test for categorical data. Time zero was defined as the date of RT completion. Primary endpoints were the cumulative incidence of CTCAE grade 3–5 events, and hospitalization-free survival. Cumulative incidence functions were used for endpoints for which death was a competing risk. Cox proportional-hazards models were used to evaluate cause-specific hazards for hospitalization-free survival. Results are presented as hazard or subdistribution hazard ratios (HRs) with 95% confidence intervals (CIs).

Confounders were chosen a priori (age, Charlson Comorbidity Index, baseline stage/grade, baseline prostate-specific antigen [PSA], androgen deprivation therapy use, RT dose/-field, and prior RP); no data-driven variable selection was applied.

Exposure groups were defined according to the clinical pathway (primary RT vs RP followed by adjuvant/salvage RT). Because treatment selection reflects the case mix, we expected differences in measured confounders (eg, age, comorbidity), and therefore probable differences in unmeasured confounders.

Statistical significance was set at a two-sided p value of < 0.05.

3. Results

During the 12-mo screening period, 347 patients were evaluated for suspected late genitourinary complications following RT. Of these, 22 were excluded after diagnostic work-up because the events were deemed unrelated to RT (eg, urinary tract infection, urolithiasis, cancer progression). The final analytical cohort comprised 325 patients with RT-attributable events. Four patients were excluded because of missing information for treatment indication, leaving 321 patients for analysis, of whom 161 (50%) underwent RP and 160 (50%) who received RT as primary treatment.

At the time of presentation, the median age was 70 yr (IQR 64–77). The median Charlson Comorbidity Index was 5 (IQR 3–6); 78% of patients had hypertension, 36% had vascular disease, 36% had diabetes, and 60% were on antiplatelet or anticoagulant therapy. Between-group differences in age and comorbidity were observed, which suggest confounding by both measured and likely unmeasured variables.

At initial PC diagnosis, median PSA was 10 ng/ml (IQR 7–15); clinical stage was cT2 in 52% and cT3-4 in 30% of patients; 18% of patients had cN+ and 7% had cM+ status. The International Society of Urological Pathology grade group was GG 1 in 15%, GG 2 in 18%, GG 3 in 27%, and GG 4–5 in 50% of patients (Table 1).

Table 1 – Distribution of demographics and disease characteristics

Variables	RT only (n = 160)	Adjuvant/early sRT after RP (n = 105)	sRT after RP (n = 56)	p value [a]
Median age at diagnosis, yr (IQR)	76 (71–79)	66 (61–70)	65 (60–69)	**<0.001**
Median CCI at AE onset (IQR)	6 (4–7)	3 (2–5)	3 (2–5)	**<0.001**
Hypertension at AE onset, n (%)	134 (84)	78 (74)	39 (70)	**0.04**
Vascular disease at AE onset, n (%)	70/159 (44)	28/101 (30)	16 (29)	**0.01**
Neurological disease at AE onset, n (%)	23/158 (15)	9/104 (9)	3 (5)	0.1
Diabetes at AE onset, n (%)	75 (47)	30 (29)	12 (21)	**<0.001**
AC/AP use at AE onset, n (%)	105 (66)	54 (51)	28 (50)	**0.03**
Smoking status at AE onset, n (%)				0.6
Nonsmoker	70/159 (44)	47 (45)	28 (50)	
Active smoker	28/159 (18)	23 (22)	13 (23)	
Former smoker	61/159 (38)	35 (33)	15 (27)	
Median PSA at diagnosis, ng/ml (IQR)	11.5 (7.8–17)	8.4 (6.8–13.5)	9 (6–13)	**0.008**
Clinical tumor stage at diagnosis, n (%)				**<0.001**
cT1	44/158 (28)	6/101 (6)	7/53 (13)	
cT2	63/158 (40)	66/101 (65)	31/53 (58)	
cT3	45/158 (28)	27/101 (27)	15/53 (28)	
cT4	6/158 (4)	2/101 (2)	–	
cN+ stage at diagnosis, n (%)	35/158 (22)	21/99 (21)	2/52 (4)	**0.004**
cM+ stage at diagnosis, n (%)	21 (13)	2 (2)	-	**<0.001**
Biopsy grade group at diagnosis, n (%)				**0.04**
Grade group 1	13/157 (8)	2/99 (2)	3/53 (6)	
Grade group 2	26/157 (17)	23/99 (23)	5/53 (9)	
Grade group 3	33/157 (21)	30/99 (30)	20/53 (38)	
Grade group 4	74/157 (47)	36/99 (36)	19/53 (36)	
Grade group 5	11/157 (7)	8/99 (8)	6/53 (11)	

AC/AP = anticoagulant/antiplatelet; AE = adverse event; RT = radiation therapy; sRT = salvage RT; IQR = interquartile range; CCI = Charlson Comorbidity Index; RP = radical prostatectomy

p-values reported in bold are statistically significant (< 0.05).

[a] p values for global comparison among the three groups.

RT was administered as primary treatment in 50%, as adjuvant/early salvage after RP in 33%, and as delayed salvage therapy in 17% of patients. In the postprostectomy group, the median time from RP to RT was 8 mo (IQR 4–24).

Table 2 details the RT data. The median dose delivered was 68 Gy (IQR, 60–72), and treatment lasted for longer than 5 wk in 55% of patients. The median time from RT to urgent consultation for an RT-related complication was 24 mo (IQR 9–58). At admission, genitourinary toxicity was CTCAE grade 1 in 27%, grade 2 in 30%, and grade 3–5 (severe or life-threatening condition) in 43% of patients (Supplementary Fig. 1).

A total of 131 patients required hospitalization. The hospitalization-free survival rate decreased from 86% (95% CI 79–91%) at 12 mo to 42% (95% CI 33–50%) at 60 mo (Fig. 1). Median follow-up for event-free patients was 15 mo (IQR 5–29). Multivariable analysis results for predictors of hospitalization are detailed in Supplementary Table 1.

We observed higher subdistribution hazard ratios for severe events in the primary RT group than in the group receiving postoperative RT (Fig. 2A, confirmed by subgroup analysis by RT setting in Fig. 2B; $p < 0.001$). Age at diagnosis was associated with severe events (Supplementary Table 2).

The percentage of patients who did not require major surgery for management of RT-related complications decreased from 81% (95% CI 76–97%) at 12 mo after RT to 66% (95% CI 48–79%) at 60 mo. The distribution of management strategies differed among the treatment settings (Table 2). Cox proportional-hazard model results for predictors of major surgical treatment are reported in Supplementary Table 3.

4. Discussion

Data from the IRRADIaTE registry highlight a substantial long-term burden of late genitourinary toxicity after prostate RT. Because the registry includes only patients who presented with complications, our results describe the burden among symptomatic men rather than the incidence among all RT recipients.

Although the incidence of severe genitourinary events was higher in the primary RT group, this signal is susceptible to confounding by indication and selection. Men who received primary RT were older and had more comorbidities: if differences in measured confounders imply differences in unmeasured confounders, we cannot assume that multivariable adjustment eliminated bias.

Management of localized PC is centered on two main curative approaches: RP and RT. Comparisons between these modalities often focus narrowly on short-sighted functional outcomes, and portray RT as less invasive. While surgery is associated with higher immediate rates of urinary incontinence and erectile dysfunction, this perception may underestimate the delayed and sometimes severe toxicity burden associated with RT, which can appear years after treatment. [16].

Clinical experience suggests that RT-related sequelae are neither rare nor trivial. Complications such as LUTS, obstructive uropathy, fistulas, and strictures can severely

Table 2 – Distribution of RT therapy data, toxicities, and management

Variable	RT only (n = 160)	Adjuvant/early sRT after RP (n = 105)	sRT after RP (n = 56)	p value [a]
Median time to RT after surgery, mo (IQR)	–	6 (3–16)	22 (6–60)	**<0.001**
Median RT dose, Gy (IQR)	70 (60–74)	66 (60–70)	66 (40–70)	**<0.001**
RT dose >60 Gy, n (%)	82/126 (65)	58/86 (67)	26/38 (68)	0.9
RT duration >5 wk, n (%)	84/156 (54)	66/103 (64)	25/55 (45)	0.06
RT approach, n (%)				**0.04**
Cyberknife	6/158 (3.8)	2/101 (2)	1/55 (1.8)	
External image guidance	152/158 (96)	94/101 (93)	51/55 (93)	
Cyberknife and external image guidance		5/101 (5)	3/55 (5.5)	
RT fields, n (%)				**0.001**
Prostate/prostatic fossa	80 (50)	37/105 (35)	20 (36)	
Pelvic LNs			2 (3.6)	
MDT	2 (1.3)			
Prostate/prostatic fossa and pelvic LNs	61 (38)	62/105 (59.1)	31 (55)	
Prostate/prostatic fossa and MDT	4 (2.5)		2 (3.6)	
Pelvic LNs and MDT		2/105 (1.9)		
Prostate/prostatic fossa, pelvic LNs, and MDT	13 (8.1)	4/105 (3.8)	1 (1.8)	
Adjuvant ADT, n (%)	136/159 (85)	71/105 (67)	45/55 (82)	**0.02**
Continence after RT, n (%)				**<0.001**
Safety pad	22/154 (14)	34/98 (35)	12/49 (25)	
1–2 pads/d	24/154 (26)	21/98 (21)	11/49 (22)	
>2 pads/d	20/154 (13)	22/98 (22)	9/49 (18)	
LUTS after RT, n (%)				0.08
Voiding phase (obstruction)	22/158 (14)	14/104 (13)	12/53 (23)	
Filling phase (urgency/frequency)	66/158 (42)	61/104 (59)	25/53 (47)	
Both	22/158 (14)	11/104 (11)	5/53 (9)	
Median time to admission (IQR)	19.5 (9–45)	24 (9–66)	28 (11–75)	0.2
Median GARM score (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.1
CTCAE AEs, n (%)				**0.04**
Grade 1	52/147 (35)	21/101 (21)	9/54 (17)	
Grade 2	36/147 (25)	38/101 (38)	17/54 (31)	
Grade 3	40/147 (27)	32/101 (32)	18/54 (33)	
Grade 4	18/147 (12)	10/101 (10)	9/54 (17)	
Grade 5	1/147 (0.7)		1/54 (2)	
Management, n (%)				0.05
Conservative	59/128 (46)	47/101 (46.5)	14/46 (30.4)	
Nonsurgical (eg, hyperbaric therapy, drain)	7/128 (5)	11/101 (10.9)	7/46 (15.2)	
Endoscopic	49/128 (38)	26/101 (26)	16/46 (35)	
Major surgery	13/128 (10)	17/101 (17)	9/46 (20)	
Median PSA at AE consultation, ng/ml (IQR)	0.42 (0.05–2)	0.01 (0.001–0.2)	0.1 (0–0.06)	**<0.001**

AE = adverse event; RT = radiation therapy; sRT = salvage RT; RP = radical prostatectomy; IQR = interquartile range; LN = lymph node; MDT = metastasis-directed therapy; ADT = androgen deprivation therapy; GARM = Genitourinary Acute Radiation Morbidity; LUTS = lower urinary tract symptoms; ER=emergency room; CTCAE = Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen.
[a] p values for global comparison among the groups.

affect a patient's quality of life and often require invasive treatments [17]. Early data from the Radiation Therapy Oncology Group provided some of the first systematic evaluations [18]. A review involving more than 2600 patients with T1–2 disease treated with EBRT revealed an overall incidence of severe complications of approximately 2% at >5-yr follow-up [19]. More recently, a 2018 international review highlighted that late grade $\geq$3 toxicity remains a concern even with modern hypofractionated regimens, with rates of 6–7%, and even higher rates of 18–31% after combined EBRT and brachytherapy. These data underscore the trade-off between treatment intensity and the toxicity burden [20]. An overall improvement in toxicity profiles over time is evident, largely because of technological refinements and more stringent dose constraints for organs at risk. Nonetheless, long-term sequelae remain clinically meaningful and should be carefully addressed during shared decision-making, particularly for patients with longer life expectancy.

In our study, the time between RT and the need for a major surgical intervention following presentation offers insights into both the potential impact of "outdated" RT equipment and the patient's life expectancy. The longer the anticipated survival, the greater is the likelihood of late complications requiring treatment.

A relevant issue is that radiation oncology services rarely include inpatient wards, so patients experiencing post-RT complications may be admitted to other departments, potentially without direct evaluation by radiation oncologists. This organizational structure may lead to underreporting of such sequelae and limits the ability to capture the full spectrum of RT-related adverse events.

Recent work has highlighted that such complications may be more common than previously acknowledged, particularly among patients presenting to urology services or requiring hospitalization [8]. The importance of systematic assessment and documentation of the true burden of post-RT genitourinary toxicity has been emphasized [7,21–23].

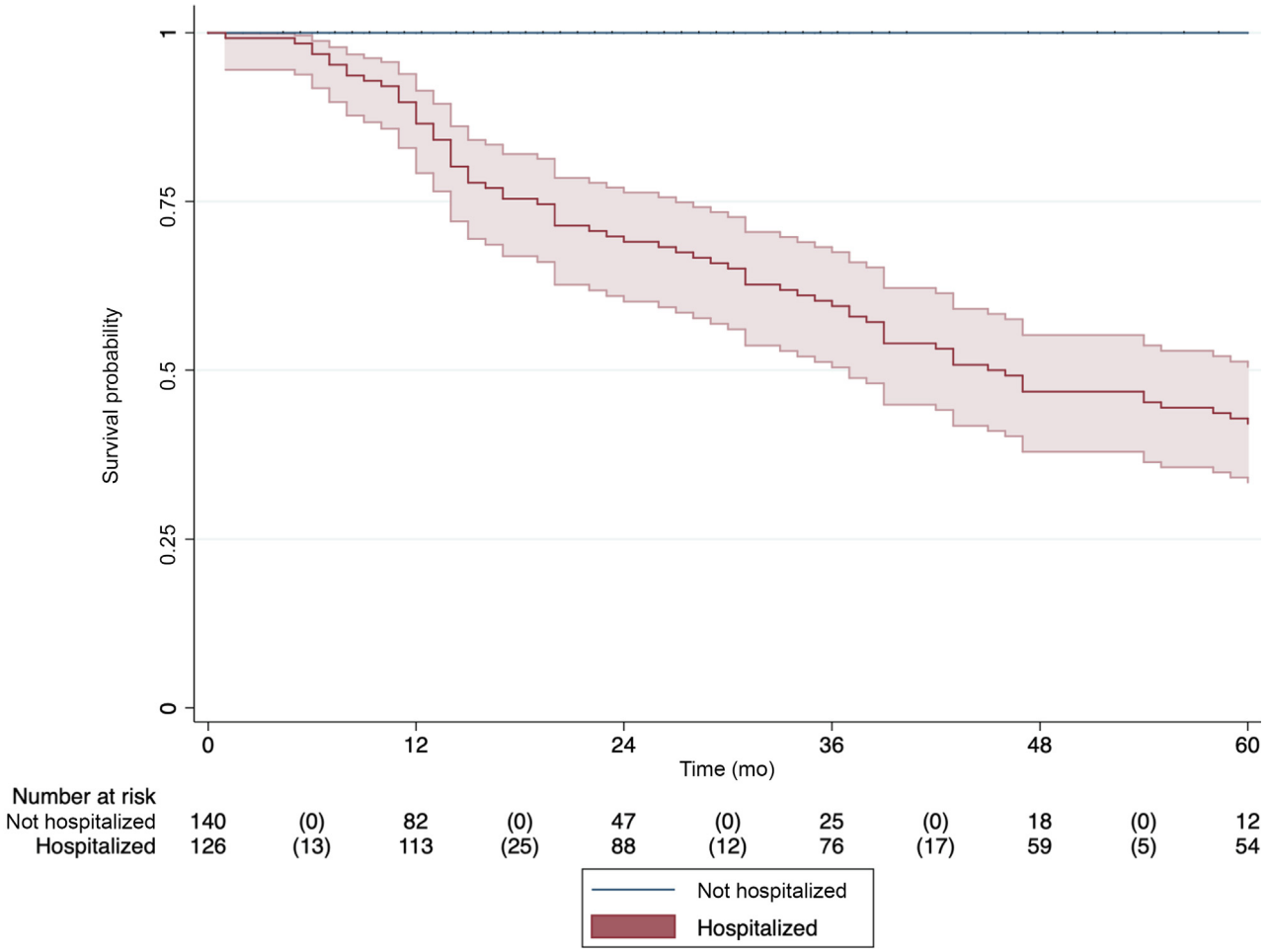


Fig. 1 – Kaplan-Meier plot of hospitalization-free survival.

In this context, our study represents one of the first prospective multicenter efforts, albeit at a national level, to systematically capture late genitourinary toxicity following prostate RT. Our findings contribute to the literature in several ways. First, we document substantial incidence of severe toxicity (CTCAE grade 3–5 in 43% of the patients presenting for care) and a notable treatment burden, with the proportion of patients avoiding major surgery for RT-related complications markedly declining from 81% at 12 mo to 66% at 60 mo after RT. Our data reveal a substantial hospital admission burden in this context: more than 40% of patients required at least one hospitalization within 5 yr of completing RT, with hospitalization-free survival declining from 86% at 12 mo to 42% at 60 mo after RT.

These data suggest a level of clinical complexity and health care resource utilization that may not be fully appreciated at the time of treatment planning. Moreover, it should be noted that among patients who initially respond to endoscopic treatment, a significant proportion are likely to experience recurrence in the short to medium term, and could potentially require further interventions. While our current data provide a snapshot of this phenomenon, future studies based on the registry will be crucial for quantification of reintervention rates and better characterization of longer-term outcomes.

Our data also raise important considerations for health-economic evaluations: while RT is often perceived as a less invasive, cost-effective option, the significant long-term burden of genitourinary complications—often requiring repeated interventions and hospitalizations—may offset the initial cost advantage in comparison to the frequently criticized robot-assisted RP. While it is undeniably true that RP incurs higher indirect costs in the immediate months following treatment (such as continence aids and medications for erectile dysfunction), a reassessment of medium- to long-term holistic cost comparisons between RP and RT would be warranted in light of our findings. Such hypotheses remain to be tested in a formal economic analysis.

Our subgroup analyses show that the cumulative risk of severe genitourinary events was significantly higher in the primary RT groups than in the postprostatectomy group with either adjuvant or salvage RT. This suggests that the clinical context and timing of RT influence the long-term toxicity profile and should therefore be taken into careful consideration during counseling. Furthermore, if one-third of patients experiencing biochemical recurrence after RP can be safely managed with active observation alone, this should be taken into account when aiming to reduce future toxicity and risks associated with salvage RT for these patients [24].

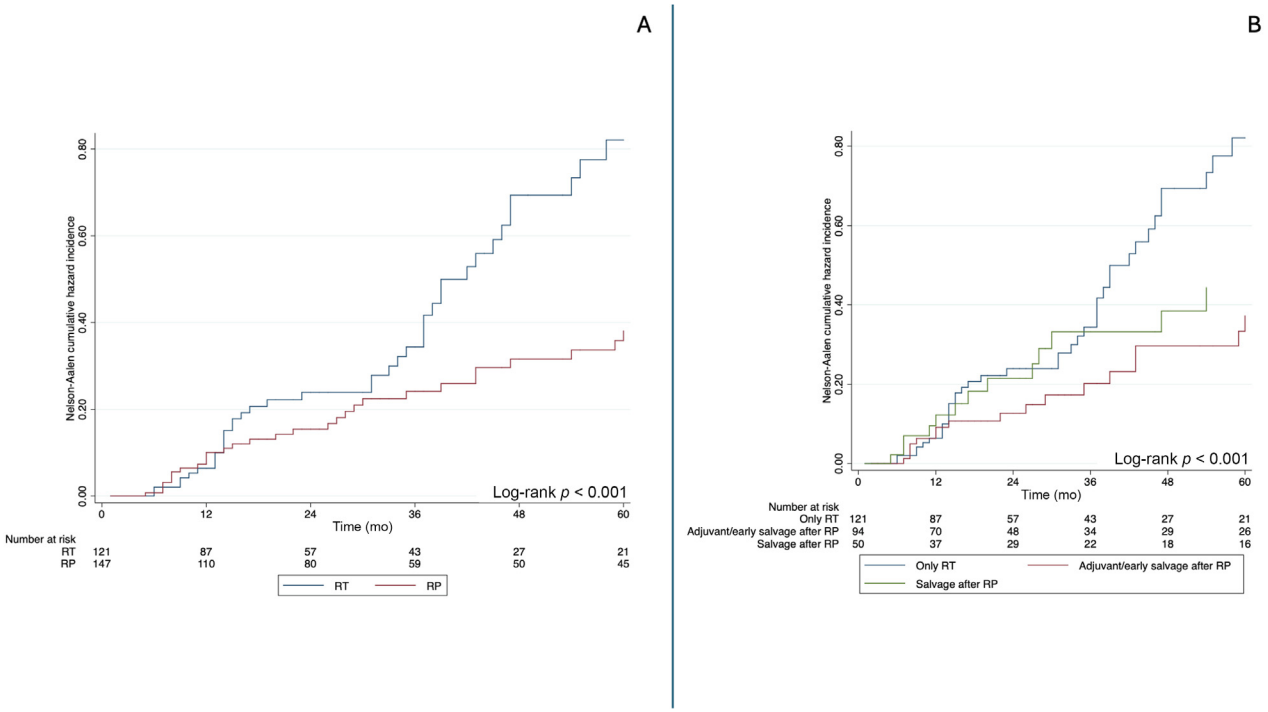


Fig. 2 – Cox proportional-hazards regression results for severe/life-threatening event–free survival, defined as grade 3–5 event according to Common Terminology Criteria for Adverse Events, stratified by (A) primary whole-gland therapy (radiotherapy [RT] vs radical prostatectomy [RP]) and (B) RT setting (primary therapy vs adjuvant/early salvage RT after RP vs salvage RT after RP). Corresponding Nelson-Aalen cumulative hazard estimates with 95% confidence intervals are provided in Supplementary Table 4.

Although current evidence often favors upfront RT for patients with locally advanced PC (cT3a, cT3b, or cN+) because of concerns about the likelihood of achieving R0 resection status [25,26], our data suggest that this approach may deserve reconsideration. Despite the limitations regarding data collection and analysis, our findings suggest that from a toxicity standpoint, patients who undergo RP followed by adjuvant or salvage RT may experience lower overall treatment-related toxicity in comparison to those treated with upfront RT. This would support the rationale for attempting RP when feasible: a complete pathological response may be achieved in a subset of patients, who, thanks to modern surgical techniques, may have decent probability of recovering urinary continence. RT could then be selectively administered only to those with unfavorable pathological features, with a significant proportion of patients thus spared from the side effects of combined-modality treatment. It is worth emphasizing that even among patients who eventually require postoperative RT, the treatment tends to be better tolerated than if it had been delivered as the primary modality from the outset, as suggested by the IRRADIaTE registry data. However, our data cannot reveal whether undergoing RP first is truly less toxic; the lower toxicity observed in the postprostatectomy group may simply reflect a disproportionate representation of more favorable cases in the study cohort.

Although RT remains a highly effective and valid treatment option, the IRRADIaTE registry data underscore that its potential for significant late toxicity must be acknowledged, even without accounting for the additional risk of secondary malignancies—such as bladder cancer—reported to be associated with prostate RT, which was not investigated in our study [27]. It has been shown that RT-associated bladder cancers exhibit distinct biological profiles that depend on latency, with long-latency tumors thought to arise from RT-induced oncogenesis [28].

This study lays a foundation for future research to identify predictors of severe toxicity, compare different RT techniques, and develop preventive strategies or optimized follow-up protocols. The main study limitation is that the prospective enrollment window was restricted to a single year; however, once a patient was identified during this period, investigators retrospectively reconstructed prior admissions related to RT-induced complications. While this approach provided valuable insights, it inherently relied on retrospective data and could not account for the unpredictable recurrence of such events over time. Another important limitation is that toxicity data and patient-reported sequelae related to RT largely reflect treatments delivered several years ago, often using equipment that may nowadays be considered outdated. With the advent of newer-generation RT machines and the increasing adoption of hypofractionated schedules, it is plausible that similar patient cohorts treated today could experience significantly lower toxicity profiles. However, these promising technologies must still be rigorously evaluated in studies with long-term follow-up before it can be assumed that they result in lower rates of late adverse effects.

A further limitation is that participating centers only captured cases of RT-related urologic complications that presented for care. While these events were numerous and clinically significant, our study probably underesti-

mates the true burden of toxicity, as some patients may have sought care at nonparticipating institutions. This registry included only patients with RT-related complications requiring urgent care, so the population-level incidence among all RT-treated men cannot be inferred owing to the lack of a reliable denominator—that is, the total number of patients treated with RT during the considered time span. This limitation is further compounded by the possibility that patients experiencing complications may present to a different center from where their primary treatment was originally delivered, or that complications from treatments performed at nonparticipating centers may have been captured in our cohort, which precludes a comprehensive estimate of the overall burden of RT-related morbidity.

We acknowledge that some clinical presentations observed in this study may not be exclusively attributable to RT; if this were the case, such events were few, generally of low grade, and rarely required surgical intervention. Importantly, all patients underwent thorough anamnesis and diagnostic evaluation, and causes clearly related to tumor progression were excluded, and thus the toxicity data reported largely reflect RT effects.

Finally, the study cohort represents a highly selected patient population, with most individuals presenting with clinically advanced disease at the time of diagnosis. These are precisely the patients for whom surgery alone rarely provides a curative opportunity; indeed, according to current EAU guidelines, RT rather than RP would typically be recommended as the preferred local treatment. This further limits the generalizability of our findings, but makes the snapshot provided by our data timely and of particular interest.

5. Conclusions

Late genitourinary toxicity after prostate RT is common among men who present for urgent care and frequently requires invasive management. Differences observed by treatment setting are associational and are probably influenced by confounding by indication; these differences should not be interpreted as treatment effects. Causal effects of treatment pathways should be evaluated using denominator-based, prospectively specified causal-inference designs. Clinical care should prioritize multidisciplinary survivorship follow-up and patient counseling on delayed toxicity.

Author contributions: Riccardo Bertolo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Bertolo.
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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2026.01.005.

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