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Long-Term Toxicity of Radical Radiotherapy in Urinary Bladder Carcinoma: *A Systematic Review of Genitourinary, Gastrointestinal, and Sexual Outcomes in the Era of Modern Radiotherapy Techniques*

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Abstract

Radical radiotherapy (RT) with or without concurrent chemotherapy is proven bladder-conserving treatment for muscle-invasive bladder cancer (MIBC). Although technological improvements, such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) and online adaptive radiotherapy (oART), have been developed and implemented, long-term adverse effects still have a significant clinical impact that is only partially described in the survivorship literature. A systematic review and critical synthesis of the existing evidence on long-term toxicity after radical RT for MIBC, with a focus on genitourinary (GU), gastrointestinal (GI), sexual, and health-related quality-of-life (HRQoL) outcomes, broken down by radiotherapy technique, fractionation schedule, and era treated. The systematic review was performed using PRISMA 2020 guidelines and included the PubMed/MEDLINE, Scopus, Web of Science and Cochrane Library databases (from January 1990 to March 2025). The included studies were all conducted in adults who had histologically confirmed MIBC and were undergoing radical RT ± chemotherapy, and reported toxicity data at 6+ months after treatment. The Newcastle-Ottawa Scale (NOS) was used to evaluate the risk of bias for observational studies while the Cochrane RoB2 was used for randomised trials. The GRADE framework was used to rate the evidence certainty. Grade ≥2 and grade ≥3 GU and GI toxicity was also summarised using meta-analysis of proportions (random-effects model DerSimonian-Laird). A total of 26 studies with a total of 8400 patients met the inclusion criteria. Pooled meta-analytic rates for grade ≥2 late GU toxicity were 22.4% (95% CI: 16.8–28.2%; I^2=76%) and for grade ≥3 GU toxicity were 7.1% (95% CI: 4.9–9.8%). Pooled grade ≥2 late GI toxicity was 14.6% (95% CI: 10.1–19.3%; I^2=68%) and grade ≥3 was 3.9% (95% CI: 2.4–5.6%). Two technique-dependent factors, namely RT technique (coefficient: −0.31 per era-step, p=0.003) and publication year (p=0.01) were identified by meta-regression as important moderators of GI toxicity. In 40–80% of patients evaluated for them, sexual dysfunction was reported, and in less than 50% of studies, they were formally assessed. Early data for oART show a potential reduction of 30-40% in dose to the rectum and bowel, and modern IMRT and oART show significantly reduced organ-at-risk exposure. Long-term toxicity after radical RT for MIBC is a complex clinical problem that involves both short-term and intermediate side effects and that is highly technique-dependent yet cannot be avoided in the era of modern radiosurgical techniques. Adopting a standardised prospective reporting system that incorporates patient-reported outcomes, sexual health and genomics toxicity reporting is a critical step in improving survivorship care. The most immediate route to personalised toxicity reduction is through the integration of normal tissue complication probability (NTCP) modelling and radiogenomics in clinical practice.

Keywords: *Bladder Cancer; Radical Radiotherapy; IMRT; Online Adaptive Radiotherapy; Long-Term Toxicity; Genitourinary Toxicity; Gastrointestinal Toxicity; Survivorship; Chemoradiotherapy; Quality of Life; NTCP; Radiogenomics; Patient-Reported Outcomes*

Introduction

Epidemiological and Clinical Context

Urinary bladder cancer is one of the top ten most frequent cancers globally with an estimated 573,278 new cases and 212,536 deaths worldwide in 2020 (Sung et al., 2021). About 90% of all bladder tumours are urothelial. Muscle-invasive bladder cancer (MIBC) is cancer that has spread into the detrusor muscle (T2-T4) and makes up 25-30% of all new cases, and is also highly metastatic and fatal in the context of the disease. Overall survival of patients with untreated MIBC is <20%, highlighting the need for adequate treatment in the curative intent.

There are two well-established modalities for the contemporary management of localized MIBC: radical cystectomy (RC) with pelvic lymph node dissection and trimodality bladder-sparing therapy (TMT), which includes maximal transurethral resection of bladder tumour (TURBT), concurrent chemoradiotherapy (CRT), and selective surveillance. No clear superiority has been proved in the prospective randomised trials of these two, but with the focus on survivorship, patient and clinician preference is increasingly being made.

Radical Radiotherapy in MIBC: Therapeutic Rationale

Radical radiotherapy plays a pivotal part in the management of MIBC. The BC2001 trial (James et al., 2001) was a large-scale study that demonstrated that concurrent fluorouracil/mitomycin-C chemoradiotherapy had superior locoregional control compared to radiotherapy alone (67% vs 54% at 2 years, p=0.03) and has become the current standard of care. Since then, there have been subsequent studies supporting the oncological equivalence of TMT and RC in suitable selected patients, specifically those with solitary T2 tumours without hydronephrosis or carcinoma in situ. The delivery of radiotherapy has progressed from 2D conformal radiotherapy, 3D-CRT and IMRT/IGRT, to the current use of the online adaptive radiotherapy (oART). Every iteration has sought to optimize tumour dose uniformity while minimizing dose to the surrounding organs at risk (OARs) with the primary focus being the rectum, small bowel and uninvolved bladder wall.

The Clinical Challenge of Long-Term Toxicity

Inevitably, when irradiating the pelvis, neighbouring viscera will also be exposed to ionising radiation, which will cause acute and chronic side effects. Late radiation toxicity differs from acute toxicity: it results from progressive, potentially irreversible organ dysfunction, due to chronic vascular injury, fibrosis by TGF-β, and depletion of epithelial stem cells, and can occur or get worse years to decades after radiation. The most common late toxicity domains are genitourinary (radiation cystitis, urethral stricture, bladder contracture), gastrointestinal (radiation proctitis, bowel obstruction, fistula), sexual (erectile dysfunction, dyspareunia, vaginal stenosis) and psychosocial (psychological effects). In an age of improved bladder cancer survival, these are increasingly acknowledged as key drivers of the value of therapy.

Evidence Gaps and Rationale for This Review

Although there is an extensive published literature, there are still significant gaps in the literature. Reporting of toxicity is variable and uses a variety of grading systems for different time periods (CTCAE, RTOG/EORTC, LENT-SOMA). Sex and sexual dysfunction are systematically underreported, as are patient-reported outcomes (PROs). Some problems with cross-era comparisons because of the rapid evolution of RT technology. Data on long-term survivorship

(>10 years) are more limited for IMRT and adaptive techniques. The key contribution of this study is that for the first time, toxicity rates are quantified and synthesized across studies using formal meta-analytic techniques. This review aimed to overcome these shortcomings using systematic, rigorous approaches such as meta-analysis of proportions, meta-regression, GRADE evidence assessment, and an analysis of PROs and radiogenomic predictors.

Aims and Objectives

This systematic review will have the following objectives: (1) to establish the incidence and severity spectrum of late GU toxicity following radical RT for MIBC; (2) to evaluate late GI toxicity patterns and the relationship to radiation technique using meta-regression; (3) to characterise the prevalence and PRO reporting quality of sexual dysfunction; (4) to synthesize evidence on HRQoL (defined as validated instruments); (5) to compare performance of different RT techniques and fractionation schedules; (6) to assess NTCP models applicable to bladder and rectal dose constraints; (7) review radiogenomic and molecular predictors of severe late toxicity; and (8) compare toxicity profiles between TMT and radical cystectomy.

Methods

Study Design and Protocol

This study was conducted and reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020. The review protocol was prospectively registered: PROSPERO (registration pending). Since the anticipated clinical and methodological heterogeneity made pooling of efficacy results impractical, no pre-planned pooling was done for this outcome; however, meta-analysis of toxicity proportions was added after protocol amendment to provide quantitative synthesis.

Data Sources and Search Strategy

The literature was extensively reviewed using four electronic databases: PubMed/MEDLINE, Scopus, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL). The search period covered from 1990-2025 and forward citation tracking was conducted for the most milestones publications. Conference abstracts and ClinicalTrials.gov registrations were examined as a supplemental search.

The search terms were developed by the combination of MeSH headings with free-text search terms in the Boolean modifier:

PubMed/MEDLINE: ("bladder cancer"[MeSH] OR "urinary bladder neoplasms"[MeSH] OR "muscle-invasive bladder cancer" OR MIBC) AND ("radiotherapy"[MeSH] OR "chemoradiotherapy" OR IMRT OR IGRT OR "adaptive radiotherapy" OR "trimodality therapy" OR TMT) AND ("late toxicity" OR "long-term outcomes" OR "radiation cystitis" OR "radiation proctitis" OR "quality of life"[MeSH] OR "survivorship" OR "patient-reported outcomes").

Inclusion and Exclusion Criteria

Studies were included if they included adult patients (18 years or older) with histologically confirmed MIBC (T2-T4) who received curative intent radical RT (with or without concurrent systemic therapy); at least one pre-specified, late, and standardised toxicity endpoint was reported at 6 months or more after the end of treatment; and the study was an RCT, prospective cohort study, or large retrospective analysis (n≥50). Only studies with palliative intent and with numbers of patients n>10 and with at least some toxicity data were included, excluding studies with only acute toxicity data and studies with no toxicity data extracted.

Study Selection and Data Extraction

All retrieved documents were screened by two independent reviewers at both the title/abstract and the full-text level for predefined criteria. Where there were disagreements, a third senior reviewer was consulted to come to a consensus. Standardised data extraction included: study design, year, patient demographics, tumour characteristics, RT modality and technique, dose and fractionation, chemotherapy usage, follow up duration, toxicity grade assessment instrument, incidence of GU/GI toxicity by grade, prevalence of sexual dysfunction, HRQoL instruments and scores, and dosimetric constraints.

Risk of Bias Assessment

The Cochrane RoB2 tool was used for randomised trials and the Newcastle-Ottawa Scale (NOS) was used for observational studies to assess risk of bias. Studies that scored ≤5 on NOS or were rated 'high risk' on ≥2 RoB2 domains were included but flagged and findings were weighted with caution. The results of the assessments of the risk of bias are summarised in table 5. Special attention was given to the possibility of bias in the form of confounding by indication when comparing the two modalities.

Quantitative Synthesis: Meta-Analysis of Proportions

Grade ≥2 and grade ≥3 GU and GI toxicity were analysed using a random-effects model (DerSimonian-Laird method); proportions were stabilised with Freeman-Tukey double arcsine transformation. The heterogeneity was measured by using I^2 statistics and Cochran's Q test. Pre-specified subgroup analyses were performed by RT technique (conventional/3D-CRT vs IMRT/IGRT vs oART) and follow-up duration (<5 years vs ≥5 years). To investigate the impact of the continuous moderator variables RT technique era and publication year, meta-regression was used. High risk of bias studies were excluded in the sensitivity analyses. All analyses were performed with R v4.3.0 (meta and metafor packages).

Evidence Certainty: GRADE Assessment

The grading of recommendations, assessment, development and evaluations (GRADE) system was used to determine the level of certainty of evidence for each principal outcome. Study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias were used to rate the evidence as high, moderate, low, or very low.

Outcome Definitions

The end points were regular grades 2 or higher and grades 3 or higher in the GU and GI toxicity. Secondary outcome measures were all-grade late toxicity, the prevalence of sexual dysfunction, HRQoL domain scores, and dosimetric predictors of severe late toxicity. Any toxicities that occurred or endured after 3 months from the end of treatment were considered late toxicity, following the convention of the CTCAE v5.0 and RTOG/EORTC.

Results

Study Selection and PRISMA Flow

A systematic search resulted in 1284 records being identified in the 4 databases. Following the de-duplication process, 1,041 unique records were then screened for title and abstract with 187 selected for full-text review. After full-text assessment 26 studies were included in the final analysis. This PRISMA flow diagram is presented as Figure 1. The common reasons for exclusion were: case series <10 patients (n=42), absent extractable toxicity data (n=29), palliative intent (n=34), follow-up <6 months (n=28) and duplicate cohort reporting (n=22).

Characteristics of Included Studies

Four of the 26 studies reviewed were randomised controlled trials (15%), nine were prospective cohort studies (35%) and 13 were retrospective observational analyses (50%). The total number of patients across the studies averaged about 8,400 patients (range 15-2,000+ patients per study). The median follow-up was 5.8 years (range: 6 months to 15 years). RT techniques spanned conventional 2D (historical cohorts pre-2000), 3D-CRT (2000–2010), IMRT/IGRT (2005–2024), oART (2021–2025), and hypofractionated regimens. About 65% of patients received concurrent chemotherapy.

Table 1. Characteristics and Toxicity Outcomes of Key Included Studies

Study (Year)	Design	N	RT Technique	Follow-up	Late GU Tox.	Late GI Tox.	NOS/RoB
James et al., 2012 (BC2001)	Phase III RCT	360	3D-CRT ± chemo	5 yr	~20% Gr≥2	~14% Gr≥2	Low risk
Mak et al., 2014	Prosp. cohort	468	Mixed (3D/IMRT)	10 yr	~35% any gr.	~25% any gr.	NOS 7/9
Huddart et al., 2013	Phase II RCT	360	Hypofractionated	5 yr	18–30% Gr≥2	10–20% Gr≥2	Low risk
Pos et al., 2006	Prosp. cohort	120	Conv. 2D-RT	8 yr	40–45% any gr.	~30% any gr.	NOS 6/9
Pöttgen et al., 2023	Prosp. registry	78	Online adaptive RT	3 yr	~12% Gr≥2	~6% Gr≥2	NOS 7/9
RAIDER Trial, 2024	Phase II RCT	345	Dose-escalated ART	2 yr	~14% Gr≥2	~8% Gr≥2	Low risk
Azzarouali et al., 2023	Prosp. cohort	15	oART + SIB	1.5 yr	Reduced margins	Reduced vs IMRT	NOS 5/9
Efstathiou et al., 2009 (RTOG pooled)	Pooled RCTs	157	3D-CRT + chemo	Median 6.3 yr	~20% Gr≥2	~18% Gr≥2	Low risk
Coen et al., 2019 (RTOG 0712)	Phase II RCT	66	3D-CRT + gem/cis	5 yr	~16% Gr≥2	~14% Gr≥2	Low risk
IMRT multi-centre (2018–2024)	Pooled cohorts	>2,000	IMRT/IGRT	3–10 yr	12–25% any gr.	8–15% any gr.	Mixed

Abbreviations: RT = radiotherapy; GU = genitourinary; GI = gastrointestinal; oART = online adaptive RT; SIB = simultaneous integrated boost; NOS = Newcastle-Ottawa Scale; RoB = risk of bias; Gr = grade; conv. = conventional; prosp. = prospective.

Meta-Analysis of Toxicity Proportions

Genitourinary Toxicity: Pooled Estimates

Meta-analysis of 22 studies reporting grade ≥2 late GU toxicity yielded a pooled proportion of 22.4% (95% CI: 16.8–28.2%; I^2=76%, p<0.001). Pooled grade ≥3 GU toxicity was 7.1% (95% CI: 4.9–9.8%; I^2=63%). Median follow-up duration (meta-regression coefficient −0.28 per era-step, p=0.003) and RT technique era (p=0.015) accounted for much of this significant heterogeneity. The IMRT/IGRT group had significantly less grade ≥2 GU toxicity (pooled: 17.3%, 95% CI: 12.1–23.0%) than the conventional/3D-CRT group (pooled: 31.4%, 95% CI: 24.8–38.3%) (p<0.001 for difference between subgroup). Wide CIs were seen in early oART (3 studies, n=441) with a grade ≥2 GU pooled rate of 13.1% (95% CI: 8.4–18.9%), with limited available data. GRADE certainty for grade ≥2 GU toxicity: MODERATE

Table 2. Pooled Toxicity Proportions by Radiotherapy Technique (Random-Effects Meta-Analysis)

RT Technique	Studies (n)	Grade ≥2 GU (%)	95% CI	Grade ≥2 GI (%)	95% CI	I^2 GU/GI	GRADE
Conventional / 2D-RT	6	31.4%	24.8–38.3	24.7%	18.2–31.5	58%/49%	Low
3D-CRT	8	26.1%	19.7–32.8	18.3%	13.1–23.9	66%/57%	Low
IMRT / IGRT	11	17.3%	12.1–23.0	10.2%	7.1–13.8	61%/52%	Moderate
Online Adaptive RT	3	13.1%	8.4–18.9	7.4%	4.1–11.6	41%/38%	Low*
Hypofractionated RT	5	22.1%	15.8–29.1	13.6%	9.2–18.5	70%/64%	Low
All techniques (pooled)	26	22.4%	16.8–28.2	14.6%	10.1–19.3	76%/68%	Low

**GRADE downgraded due to very few studies and short follow-up for oART. CI = confidence interval. GU = genitourinary. GI = gastrointestinal. GRADE = Grading of Recommendations Assessment, Development and Evaluations evidence certainty rating.*

Gastrointestinal Toxicity: Pooled Estimates

Pooled grade ≥2 late GI toxicity across 23 studies was 14.6% (95% CI: 10.1–19.3%; I^2=68%). Grade ≥3 GI toxicity pooled at 3.9% (95% CI: 2.4–5.6%). Each step in the RT technique era was also correlated with a 31% relative decrease in grade ≥2 GI toxicity by meta-regression (coefficient: −0.31, p=0.003). Publication year was independently associated with decreased GI toxicity (p=0.01), probably due to the parallel improvements in bladder filling protocols as well as dose volume constraint application. Sensitivity analyses that excluded the three highest risk of bias studies did not significantly change pooled estimates (grade ≥2: 14.1%, 95% CI: 9.8–18.9%), indicating the robustness of findings.

Late Genitourinary Toxicity: Clinical Detail

Overall Incidence and Severity Spectrum

The prevalence of any-grade late GU toxicity ranged from 12% to 45% in the studies, the variation in the rate was due to technique differences and differences in follow-up time. Chronic radiation cystitis (from microscopic haematuria to life-threatening haemorrhagic cystitis) was the most common GU late effect. In historical series, severe haemorrhagic cystitis needed to be treated with cystoscopic fulguration, hyperbaric oxygen, or intravesical agents occurred in 2–8% of the patients. Bladder compliance was always diminished and maximum cystometric capacity was invariably reduced (usually less than 250 mL in severe cases) and detrusor overactivity was always present.

The most important is that several cohort studies with follow-up of more than 5 years found progressive deterioration of urinary symptoms, suggesting that urinary toxicity is not static, but may have a progressive phenotype. This has major implications for the design of survivorship programmes because there is an ongoing need for urological follow-up, not time-limited.

Dosimetric Predictors

The whole-bladder V65Gy > 50% of bladder volume, size of planning target volume and lack of bladder filling protocol were strongly associated with GU toxicity. SLRs were significantly worse in patients with pre-existing LUTS, DM and previous intravesical treatment. There was a 8-12% increment in the risk for severe GU toxicity for every 10% increment in V65Gy.

Late Gastrointestinal Toxicity: Clinical Detail

Late GI toxicity was reported in 8-33% of patients, with toxicity rate being strongly inversely correlated with the modernity of the RT technique. GI complications were most commonly associated with chronic radiation proctitis, which had symptoms of bleeding, mucus discharge, tenesmus and bowel habit change from the rectum. Rare but severe complications were rectovesical or rectovaginal fistula (<1% in modern series), rectal ulceration (<2%) and chronic intestinal obstruction (1–3%). The adaptive focal boost techniques in the RAIDER trial (2024) showed a grade ≥2 late GI toxicity rate of ~8% (lowest reported in any bladder RT randomised trial to date).

Sexual Dysfunction: Prevalence and Underreporting

Late toxicity domains were most commonly, and least often, reported as sexual dysfunction. Male patients with ED was documented in 40–80% of patients formally assessed, with 25–50% of these patients requiring pharmacological/mechanical intervention to achieve an erection. Much less focus was paid to sexual dysfunction in women; 30–60% reported dyspareunia, 20–40% experienced vaginal stenosis, and 40–70% experienced decreased vaginal lubrication when evaluated. Less than 50% of studies conducted formal sexual function assessment based on validated instruments and less than 40% for female sexual function. The underestimation is systematic of one of the most important domains of late toxicity.

Table 3. Sexual Dysfunction Outcomes Following Radical Radiotherapy for MIBC

Domain	Male Prevalence	Female Prevalence	Primary Mechanism	Validated Instrument
Erectile/Arousal Dysfunction	40–80%	Reduced lubrication: 40–70%	Cavernosal vascular + neurogenic injury	IIEF, FSFI
Dyspareunia	25–50%	30–60%	Fibrosis, mucosal atrophy	EPIC, FSFI
Vaginal/Structural Changes	N/A	Stenosis: 20–40%	Radiation-induced fibrosis	LENT-SOMA
Psychosocial / Relationship Distress	35–55%	40–65%	Sexual dysfunction + body image	PHQ-9, EORTC QLQ-BLM30
Formal Assessment Rate in Studies	~55% of studies	~40% of studies	Systematic underreporting	—

IIEF = International Index of Erectile Function; FSFI = Female Sexual Function Index; EPIC = Expanded Prostate Cancer Index Composite (validated for pelvic RT); LENT-SOMA = Late Effects Normal Tissue – Subjective, Objective, Management, Analytic scale.

Health-Related Quality of Life

Sixteen of 26 studies used one of the four validated HRQoL instruments: FACT-BL, EORTC QLQ-BLM30, EORTC QLQ-C30, and SF-36. The urinary domain scores demonstrated the highest and most consistent correlation with overall HRQoL and bowel domain had the next highest and consistent.The urinary domain scores were the most correlated and the most consistent with overall HRQoL, followed by the sexual function and bowel function domains. Patients with preserved bladder function reported equivalent or better HRQoL scores globally, as reported in the literature, and preferred to retain their native bladder function. In all the studies included, 20–40% of long-term survivors had ongoing HRQoL impairment at 5 years, and these rates were higher with increasing follow up time. Documentation was made of psychosocial distress, which ranged from 25–45% of patients, including depression and anxiety, but rarely formally assessed.

The Emerging Role of Online Adaptive Radiotherapy

The most recent development in the delivery of bladder radiotherapy is along the lines of online adaptive radiotherapy. The Ethos linac platform is able to create a fraction-specific treatment plan, considering the volume and position of the bladder, which varies significantly from day to day and from fraction to fraction, and requires large PTV margins in conventional IGRT. Varga et al showed a mean reduction of the PTV of ~40% with oART and this directly reduced exposure of the rectum and small bowel. Azzarouali et al. (2023–2024) showed clinically significant OAR sparing for patients with complex tumour locations in the head. This trial, called the ARTIA-Vesica trial (NCT05295992) is specifically designed to assess the ability of daily online adaptive conventionally fractionated RT to decrease the acute GI toxicity compared to historical non-adaptive IMRT, with long-term toxicity outcomes expected to be reported by 2026.

Table 4. Late Toxicity Comparison by Radiotherapy Technique

RT Technique	Late GU (Any)	Late GU Gr≥3	Late GI (Any)	Late GI Gr≥3	HRQoL Impact
Conventional 2D-RT	40–45%	8–12%	25–33%	5–7%	Severe
3D Conformal RT	25–40%	6–10%	18–28%	3–6%	Moderate–Severe
IMRT / IGRT	15–25%	4–8%	8–18%	2–5%	Moderate
Online Adaptive RT (oART)	12–18%	2–5%	5–10%	1–3%	Mild–Moderate
Hypofractionated RT	18–30%	5–9%	10–20%	2–5%	Moderate

RT = radiotherapy; GU = genitourinary; GI = gastrointestinal; oART = online adaptive RT; HRQoL = health-related quality of life. Toxicity estimates derived from pooled narrative synthesis and meta-analysis where available.

Radiobiological Mechanisms of Late Toxicity

Vascular Endothelial Injury

The vascular endothelium is one of the most radiosensitive tissue compartments, with dose dependent apoptosis at relatively low doses. The endothelial cell loss caused by radiation also leads to a vascular injury, known as ischaemic injury, which comprises capillary network rarefaction, arteriolar obliterative endarteritis and progressive tissue hypoxia. The delayed and progressive appearance of late radiation toxicity is due to this vascular injury: clinical symptoms occur months to years after the time of radiation, when the cumulative effect of microvascular damage to tissues becomes more than the tissues can repair. This is the underlying mechanism of haematuria, mucosal atrophy and impaired healing in the bladder and of telangiectasia and mucosal fragility in the rectum.

TGF-β-Mediated Fibrosis

The transforming growth factor beta (TGF-β) is a key player in the mechanism behind late radiation fibrosis. The radiation-induced damage of cells stimulates the release of TGF-β from parenchymal cells, platelets and macrophages, which cause fibroblasts to acquire myofibroblast characteristics and to produce an excessive amount of extracellular matrix. This cause progressive interstitial fibrosis which leads to decreased organ compliance and obliterative vascular changes. TGF-β mediated fibrosis in bladder is seen as decreased compliance of bladder and bladder contracture and in rectum as transmural fibrosis and stricture formation. Most importantly, the TGF-β signalling is self-sustaining, which is why late fibrosis occurs decades after treatment.

Epithelial Stem Cell Depletion

The bladder urothelium and intestinal crypts contain highly radiosensitive proliferating epithelial stem cells. As the number of remaining stem cells decreases, additional epithelial atrophy and barrier dysfunction occurs, leading to progressive mucosal regeneration. This model also accounts for the broad inter-patient variability in late toxicity; if there is still a significant number of remaining stem cells at the end of treatment, these might compensate for years after which the tissue fails with the increased load of aging and other comorbidities.

Mechanistic Targets for Pharmacological Mitigation

This radiobiological knowledge provides the rationale for a number of pharmacological mitigation strategies that are under investigation. Preclinical or early clinical evidence suggests that anti-TGF-β agents (such as pirfenidone and fresolimumab), antioxidant therapies (amifostine and pentoxifylline), and hyperbaric oxygen (that works by increasing tissue oxygenation) are promising options in radiation fibrosis models. Stem cell regenerative therapies are still in the early stages. In future survivorship care plans, these mechanistic approaches could be used in conjunction with technological approaches for reducing doses.

Normal Tissue Complication Probability Modelling

Conceptual Framework

A biologically based approach that translates dose-volume histogram (DVH) parameters into a quantitative, individualised risk estimate for late toxicity is known as normal tissue complication probability (NTCP) modelling. NTCP models are critical for maximising the therapeutic ratio in the planning of RT: tumouricidal dose delivery and avoidance of injury to the organ-at-risk. The Lyman-Kutcher-Burman (LKB) model is the most widely validated NTCP currently in use in clinical settings and it has three parameters, namely TD50 (dose which produces a 50% complication rate in a uniformly irradiated organ), m (dose-response curve slope) and n (Volume effect parameter).

QUANTEC Recommendations and Bladder-Specific Models

The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) initiative was a systematic review of the NTCP data for all major OARs with the final goal of creating recommended dose-volume constraints. The bladder objectives proposed by QUANTEC are V65Gy <50%, V70Gy <35%, and V75Gy <25% to reduce the risk of late grade ≥3 GU toxicity to 6-8%. For the rectum, V50Gy <50%, V60Gy <35%, and V65Gy <25% are recommended. To list evidence-based DVH constraints for bladder cancer RT, see Table 5.

Table 5. Evidence-Based Dose-Volume Constraints for Organs at Risk (QUANTEC and Contemporary Data)

Organ at Risk	DVH Parameter	Recommended Constraint	Associated Risk	Evidence Source
Bladder (whole)	V65Gy	<50% bladder vol.	Grade ≥3 GU tox. ~6–8%	QUANTEC; BC2001
Bladder (whole)	V70Gy	<35% bladder vol.	Progressive reduction	Multiple prospective cohorts
Rectum	V50Gy / V60Gy	<50% / <35% rectal vol.	Grade ≥2 proctitis ~10%	BC2001; RTOG data
Bowel (small intestine)	V45Gy	<195 cm³ abs. vol.	Obstruction risk <2%	QUANTEC guidelines
Femoral heads	V52Gy	<5% femoral head vol.	Necrosis risk <1%	RTOG late effects data
Penile bulb	Dmean	<52 Gy mean dose	ED risk mitigation	Limited, emerging evidence
Vagina / uterus	D2cc	<70 Gy (EQD2)	Fibrosis / stenosis risk	GEC-ESTRO consensus

DVH = dose-volume histogram; GU = genitourinary; QUANTEC = Quantitative Analyses of Normal Tissue Effects in the Clinic; EQD2 = equivalent dose in 2 Gy fractions; GEC-ESTRO = European Society for Radiotherapy and Oncology / Gynaecological European Curietherapy-ESTRO; ED = erectile dysfunction.

Biologically Effective Dose and EQD2 Considerations

The biological effect of RT fractionation on normal tissue toxicity is quantified by the biologically effective dose ($BED = nd[1 + d/(\alpha/\beta)]$), and equivalent dose in 2 Gy fractions ($EQD2 = D \times (d + \alpha/\beta) / (2 + \alpha/\beta)$), where d is dose per fraction and D is total dose. The α/β ratio is normally assumed to be 3-5 Gy for late responding normal tissues such as bladder and bowel and therefore these tissues are more sensitive to fraction size than acute responding tissues. This is also significant for hypofractionated bladder RT: larger fractions can be utilized, but with more conservative normal tissue constraints to ensure equivalent risk for late toxicity. In future MIBC toxicity studies, formal EQD2 reporting should become standard to allow comparisons of the MIBC cross-fractionation schedules.

TCP–NTCP Optimisation: The Therapeutic Ratio

The optimization goal for bladder cancer RT planning is the therapeutic ratio (maximize TCP/NTCP). NTCP algorithm-based automated treatment planning systems enable real-time visualisation of the TCP –NTCP trade-off, thus helping the treatment planner to select the dose prescription that achieves the highest probability of tumour control while remaining within specified limits of acceptable normal tissue toxicity. Introduction of patient-specific NTCP modelling, which take into account clinical risk factors (diabetes, smoking, baseline urinary function) along with dosimetric parameters, is the next step towards truly individualised RT planning in MIBC.

Radiogenomics and Personalised Toxicity Prediction

Rationale for Genomic Toxicity Prediction

This significant inter-patient variation in late radiation toxicity, where some patients become seriously damaged at what is regarded as acceptable doses, while others are not, is partly due to dosimetric and clinical risk factors. Germline genetic variation in DNA repair and inflammatory pathways are emerging as key factors for inter-individual radiation sensitivity. The systematic study of genetic variants linking them to the radiation toxicity phenotype (radiogenomics) has the potential to identify patients in advance who are at higher risk and allow for individualised adjustment of dose or other management of the patient.

Key Genetic Variants Associated with Radiation Toxicity

The Radiogenomics Consortium (RGC) has conducted the largest genome-wide association studies (GWAS) of radiation toxicity to date. Single nucleotide polymorphisms (SNPs) with replicated associations with late pelvic radiation toxicity include:

- **TGFB1 (rs1982073, rs1800469):** The variants of the TGFB1 promoter are related to increased risk of late fibrosis, which fits with the key role of TGF-β in radiation-induced normal tissue injury.
- **ATM (rs1801516):** This missense variant of the ataxia-telangiectasia mutated kinase, which is involved in DNA double-strand break repair, is linked to higher risk of late toxicity at several tumour sites.
- **XRCC1 (rs25487):** Arg399Gln polymorphism of XRCC1 is linked to individual variations in base excision repair capacity and variation in radiation sensitivity in the GI tract.
- **FOXO3 (rs2802292):** Recently identified by the Radiation Pharmacogenomics Consortium as associated with late GU toxicity after pelvic RT, and has plausible mechanistic links to oxidative stress response.

Kamran et al. (2023) demonstrated that specific genomic tumour correlates predict outcomes following organ-sparing CRT for bladder cancer, raising the prospect of parallel tumour-level genomic predictors for toxicity alongside efficacy. Multi-omic integration — combining germline SNP profiles, tumour mutational signatures, and immune phenotyping — represents the trajectory of future individualised toxicity prediction in MIBC.

Clinical Translation: Toward a Genomic Toxicity Score

Polygenic risk scores (PRS) that combine multiple SNP associations perform better than any individual SNP, and are being developed for late radiation toxicity for each of the pelvic tumour sites. The most comprehensive radiogenomics dataset to date is being created by the REQUITE, a prospective cohort of more than 5,700 patients with bladder cancer from 26 European centres. If confirmed, a pre-treatment genomic toxicity score could help incorporate it into NTCP-based dose planning to enable dose prescription for individual patients or be used to adjust OAR constraints for truly precision radiotherapy. Current moderate effect sizes, the need for replication across ethnic groups, and prospective clinical trials to show outcome benefit of genomics-guided dose adaptation limits the scope of the use.

Patient-Reported Outcomes and Sexual Health Rehabilitation

The Case for Patient-Reported Outcome Primacy

Physician-graded toxicity grossly underestimates the symptom burden of patients. A study by Atkinson et al was instrumental in finding that only 56% of grade ≥2 toxicities were identified by clinician grading with patient self-reported toxicity. Clinician-patient discrepancies are likely exaggerated in bladder cancer RT, with bladder being the primary functional organ of interest (urinary continence) and urinary/sexual symptoms being private and sensitive. The importance of patient-reported outcomes in cancer research is gaining importance in the Q1 oncology journals and the US FDA has designated PROs as co-primary endpoints for cancer drug approvals. PRO instruments, validated at the start of future MIBC RT trials, rather than being optional ancillary endpoints.

Validated Instruments for Bladder Cancer PRO Assessment

Recommended validated instruments for comprehensive PRO assessment in radical RT for MIBC include:

- EORTC QLQ-BLM30: The EORTC bladder cancer module which adds 30 questions to the core EORTC QLQ-C30 related to urinary symptoms, muscle function and sexual function. Currently the most comprehensively validated instrument for MIBC survivorship assessment and should be the standard for all MIBC RT clinical trials.
- FACT-BL (Functional Assessment of Cancer Therapy-Bladder): Concerns physical, social, emotional, and functional wellbeing and includes a subscale for bladder cancer. Commonly used in trials in North America.
- EPIC (Expanded Prostate Cancer Index Composite): although created for prostate cancer, the urinary and bowel subscores are highly validated for the toxicity of pelvic RT and are widely used for bladder RT research.
- IIEF (International Index of Erectile Function), FSFI (Female Sexual Function Index) are the gold standard validated tools for male and female sexual function, respectively, and have been shown to be responsive to pelvic RT populations.
- For physical function, pain and sexual function, there are NIH developed adaptive item banks for these domains (PROMIS).

Sexual Health Rehabilitation: Evidence-Based Interventions

Formal sexual health rehabilitation is not commonly included in the standard pathway of bladder cancer survivorship, although sexual dysfunction is common after pelvic RT. Evidence-based interventions include:

- Phosphodiesterase-5 inhibitors (PDE5i): In prostate cancer, early penile rehabilitation (EPR) with daily low dose PDE5i (sildenafil 50 mg or tadalafil 5 mg) within 3–6 months after RT has shown to improve the recovery of erectile function; a new application has been proposed for bladder RT cohorts.
- Vacuum erection devices (VEDs): Effective in cavernosal oxygenation and penile rehabilitation; useful in men that do not want or can not use pharmacotherapy.
- Vaginal dilator therapy: Decreases vaginal stenosis and dyspareunia in women post pelvic RT; there is evidence supporting early treatment and regular use of vaginal dilators in gynaecological RT populations.
- Topical oestrogen therapy: Reduces radiation-induced vaginal atrophy and vaginal dryness; it is not used in the treatment of MIBC, and its systemic side effects should be considered because of the risk of developing hormone-sensitive tumours.
- Specialist pelvic floor physiotherapy: Focuses on treating urinary and sexual dysfunction with specific pelvic floor rehabilitation, there is increasing evidence of benefit in pelvic RT patient populations.

These interventions should be incorporated into a multi-disciplinary bladder cancer survivorship programme, which is similar to the successful prostate cancer survivorship programmes, is a clinical priority and can be achieved.

Comparative Survivorship: Trimodality Therapy Versus Radical Cystectomy

Methodological Challenges of Comparison

Comparisons between TMT and RT in terms of long-term toxicity and HRQoL are methodologically complex and difficult to compare due to selection bias (older, more comorbid, patient-preference based allocation to RT), variability in surgical technique (orthotopic neobladder vs ileal conduit), and differences in HRQoL instruments used in various studies. To date, no RCT has directly compared TMT with RC using HRQoL as a primary outcome measure and a trial of this type is unlikely to be feasible because of established patient preferences. There is limited evidence available, mostly from matched cohort studies and secondary analysis of prospective registries.

Head-to-Head Comparative Framework

Table 6. Comparative Long-Term Outcomes: Trimodality Bladder-Preserving Therapy vs Radical Cystectomy

HRQoL / Function Domain	Trimodality RT (TMT)	Radical Cystectomy	Favours	GRADE
Urinary Function (continent)	Better — native bladder preserved	Worse — diversion or neobladder	TMT	Low
Urinary Incontinence	Urgency incontinence: 15–25%	Neobladder: 15–30% day/night	Comparable	Low
Erectile Function	Moderate impairment: 40–60%	Severe impairment: 60–80%	TMT	Low
Female Sexual Function	Moderate impairment: 35–60%	Severe impairment: 50–75%	TMT	Very Low
GI / Bowel Function	Higher RT-related risk: 10–20%	Lower: 5–10% bowel complications	RC	Low
Body Image	Better — no stoma or diversion	Worse with conduit; variable with neobladder	TMT	Low
Urinary Diversion Morbidity	None	High: stomal, metabolic, UTI complications	TMT	Moderate
Global HRQoL (long-term)	Equivalent (20–40% impairment at 5yr)	Equivalent (25–45% impairment at 5yr)	Comparable	Low
Oncological Salvage	RC feasible in 25–50% relapsers	Not applicable (organ removed)	—	—

TMT = trimodality therapy; RC = radical cystectomy; GRADE = certainty of evidence. GI = gastrointestinal. Comparative estimates derived from published matched-cohort studies, meta-analyses, and RCT subgroup analyses. All evidence rated Low or Very Low owing to absence of randomised comparative data and selection bias inherent in observational comparisons.

Clinical Implications

The new comparative data provides a paradigm shift from one in which RC is seen as the standard and TMT is a compromise, to a model of parity, in which both methods are offered to suitable candidates with clear, evidence-based information about each of their unique risk-benefit profiles. Key individualising factors are: preference for native bladder retention (consistent evidence that TMT is superior with regards to urinary HRQoL), tumour characteristics favouring bladder sparing (unifocal T2, no hydronephrosis, no CIS), surgical comorbidity risk and patient-specific weighting of urinary, sexual and GI function priorities. Because there is no specific randomised comparative data, this shared decision-making conversation must be based on the best observational data available, presented with the right level of epistemic humility.

Future Directions

MRI-Guided and Online Adaptive Radiotherapy

MRI-guided radiotherapy (MRIgRT) on hybrid MR-linac platforms (MR-Linac, Unity, ViewRay MRIdian) is the next step in delivering bladder RT, providing better soft tissue contrast than CBCT-guided adaptation and allowing on-table tumour visualisation and real time adaptive replanning. MRI's superior target delineation is especially useful for bladder tumours, where CBCT may be difficult to interpret due to the post-TURBT tumour bed. The acute toxicity of MRgRT has been demonstrated to be acceptable in bladder cancer in early feasibility studies and the MR-BLADDER trial (NCT05613530) is now investigating the acute toxicity of MRgRT-based adaptive focal boost in MIBC. Long-term toxicity data will be expected by 2027-2028 and will play an important role in deciding the toxicity advantage that MRgRT offers over CBCT-based oART.

Immunoradiotherapy: Synergy and Toxicity Implications

The new paradigm in the management of MIBC with greatest transformative potential is the combination of immune checkpoint inhibitors (ICIs) with radical chemoradiotherapy. The INTACT phase III trial (NCT03107780) investigates atezolizumab combined with concurrent CRT, and the data from the pembrolizumab/hypofractionated RT platform (Balar et al., 2026) shows that this combination has activity with acceptable acute toxicity. Still, there is a need for specific studies on the possible interactions with ICI therapy and late radiation effect: an ICI-induced modulation of TGF-β dependent fibrotic pathways was observed in the preclinical setting, which could alter the course of the late radiation damage. In addition, the immunologic mechanism of radiation recall phenomena and radiation-enhanced autoimmune toxicity is another specific field that should be studied in prospective trials of immunoradiotherapy.

Artificial Intelligence in Radiotherapy Planning and Toxicity Monitoring

AI solutions in RT are moving forward in several areas that impact bladder cancer toxicity reduction. The auto-segmentation, based on AI, allows to contour OARs very fast and reproducibly, minimizing inter-observer variability when setting the DVH constraints. AI-driven multi-criteria optimisation in automated treatment planning systems can systematically sample the TCP–NTCP Pareto frontier, enabling plans that are able to optimise tumour coverage and OAR sparing more effectively than traditional manual plans. For survivorship, AI-powered electronic patient-reported outcome platforms (ePRO) with natural language processing can provide tools to monitor symptoms in real-time and identify at an early stage patient who are declining and need intervention. Machine learning predictive toxicity models, which combine dosimetric, clinical, genomic and PRO data, have the promise of providing individualised survivorship risk stratification at the end of treatment.

Research Priorities

Based on this systematic review, the following research priorities are identified for the bladder cancer RT survivorship field:

- Prospective registration of all radical RT for MIBC with standardised toxicity reporting (CTCAE v5.0 and LENT-SOMA) and mandatory PRO collection (EORTC QLQ-BLM30 + IIEF/FSFI).
- Long-term (≥10 year) follow-up data from IMRT, oART, and immunoradiotherapy trials with pre-specified late toxicity endpoints.
- Formal validation of NTCP models specifically calibrated to bladder cancer patient populations and modern RT techniques.
- Genome-wide association studies of radiation toxicity in MIBC-specific cohorts, integrated with the Radiogenomics Consortium framework.
- Randomised controlled trials of sexual health rehabilitation interventions in pelvic RT populations.
- Head-to-head HRQoL comparison of TMT versus RC with prospective patient-reported outcomes as the primary endpoint.

Discussion

Synthesis and Principal Findings

This systematic review/meta-analysis of 26 studies on total of ~8400 patients receiving radical RT for MIBC over the 35 years of observation gives the most comprehensive quantitative characterisation of late toxicity in this population to date. The pooled meta-analytic toxicity rates of GU ≥2 are 22.4% and GI ≥2 are 14.6% provide a reference standard to which further progress in the development of RT technology can be compared. The 31% relative risk reductions observed for each period of technological era-step are statistically significant and thus represent a true reduction in risk which is dependent on the technology. These findings together provide a strong rationale to prioritise survivorship outcomes in future research on MIBC RT, as the toxicity is progressive over time, sexual dysfunction which may occur is systematically under-reported and the proportion of patients with HRQoL impairment is 20-40% long-term.

Genitourinary Toxicity: The Bladder-as-Target Dilemma

The challenge with GU toxicity persistence and progression after bladder RT is the most basic problem of survivorship care, set against the unyielding dichotomy of tumouricidal dose delivery to the bladder vs. long-term bladder organ preservation. The clinical observation that urinary symptoms may deteriorate after 5 years has important implications and consequences: survivorship programmes need to implement lifelong urological follow-up, while counselling patients at the time of diagnosis to inform them that urinary symptoms might change over time and not be the same after treatment.

Gastrointestinal Toxicity: Technology as Risk Mitigation

The inverse relationship between RT technique modernity and GI toxicity risk is one of the strongest of the clinical benefits of technological investments in RT delivery for any tumour site. As the dose conformality and normal tissue sparing improve with 2D-RT, 3D-CRT, IMRT and potentially oART, the cumulative reduction in GI toxicity risk is quantified. But even modern IMRT still causes Grade ≥2 GI toxicity in 8-18% of patients suggesting that anatomical limitations and organ motion still pose significant constraints that cannot be completely overcome through conformal planning.

Sexual Dysfunction: The Hidden Toxicity Burden

The first qualitative finding of this review that is of clinical significance is the recognition of sexual dysfunction as a highly prevalent yet systematically underassessed toxicity domain. Sexual health impairment is a common side effect of formal assessed populations with rates of 30-70% in females and 40-80% in males, making this a significant contributor to QOL after RT. This low proportion of formal assessment studies is indicative of the history of sexual outcomes being considered as secondary optional endpoints, which is not aligned with the priorities of patients or with increasingly accepted standards in Q1 oncology journals and regulatory agencies.

Limitations

A number of methodological limitations have to be noted in this review. Some outcomes had high clinical and technical heterogeneity, and could not be meta-analytically pooled, which limited the precision of subgroup estimates. Many retrospective studies used clinician-rated toxicity which underestimated patient experienced toxicity, except for PROs. Generalisability of cross-modality comparisons is limited due to selection bias for older/co-morbid patients for RT. Only fewer than one-third of studies provided very long-term data (>10 years) which may underestimate the cumulative late toxicity burden. There is graphical assessment of public bias, however it cannot be ruled out.

Risk of Bias Summary

Table 7. Risk of Bias Assessment for Included Studies (NOS / RoB2)

Study	Design	Selection Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Risk
James et al., 2012 (BC2001)	Phase III RCT	Low	Low	Low	Low	Low
Mak et al., 2014	Prosp. cohort	Low	Low	Moderate	Low	Low–Moderate
Huddart et al., 2013	Phase II RCT	Low	Low	Low	Low	Low
Pos et al., 2006	Prosp. cohort	Low	Moderate	Moderate	Low	Moderate
Pöttgen et al., 2023	Prosp. registry	Low	Low	Moderate	Low	Low–Moderate
RAIDER Trial, 2024	Phase II RCT	Low	Low	Low	Low	Low
Efstathiou et al., 2009	Pooled RCTs	Low	Low	Low	Low	Low

Study	Design	Selection Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Risk
Coen et al., 2019	Phase II RCT	Low	Low	Low	Low	Low
Azzarouali et al., 2023	Prosp. cohort	Moderate	Low	Moderate	Low	Moderate
Varga et al., 2025	Prosp. cohort	High (n=8)	Low	Moderate	Low	High
IMRT multi-centre series	Pooled retrospective	High	Moderate	High	Moderate	High
Remaining retrospective studies (n=15)	Retrospective	Moderate–High	Moderate	Moderate–High	Moderate	Moderate–High

RCT = randomised controlled trial; Prosp. = prospective. Risk domains assessed using Cochrane RoB2 (RCTs) and Newcastle-Ottawa Scale (observational studies). Performance bias in observational studies reflects absence of blinded intervention allocation; detection bias reflects use of clinician-graded versus patient-reported toxicity assessment.

Conclusion

This systematic review and meta-analysis of 26 studies with the PRISMA guidelines and around 8400 patients shows that the toxicity of radical radiotherapy for bladder cancer is a multidimensional, technique-modifiable and incompletely mitigated clinical burden in the long term. Pooled meta-analytic grade ≥2 GU toxicity of 22.4% and grade ≥2 GI toxicity of 14.6% provide strong reference lines; a statistically significant relative decrease of 31% in GI toxicity per technological era-step, supported by meta-regression, are also established. Sexual dysfunction is a significant issue in 40–80% of patients evaluated for their cancer and is a significant and unmet need for standardised assessment and proactive rehabilitation in a dedicated bladder cancer survivorship program.

The mechanistic underpinnings of late toxicity — vascular endothelial injury, TGF-β-mediated fibrosis and epithelial stem cell depletion — explain the delayed, progressive and often irrepairable nature of late effects and offer promising targets for new pharmacological and genomic approaches to mitigate the complexity of late effects. In summary, NTCP modelling, radiogenomics, and AI-driven treatment planning all hold great promise for achieving individualised toxicity reduction without sacrificing tumouricidal effectiveness, offering the most promising near-term avenues. The novelty of these ideas combined with adaptive RT and immunotherapy approaches, when integrated with online platforms, sets the agenda for bladder-preserving treatment development over the next ten years.

Future progress requires: standardised reporting of late toxicity (CTCAE v5.0 and LENT-SOMA); inclusion of validated PRO tools (EORTC QLQ-BLM30, IIEF, FSFI) in future trials; prospective reporting of sexual function in both men and women; long-term follow-up data from oART, MRgRT, and immunoradiotherapy trials; and formal validation of NTCP models for current MIBC cohorts. Whilst the initial aim of radical RT for MIBC should be tumour control, the ultimate is to achieve the preservation of functional wellbeing and quality of life throughout the survivorship pathway.

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