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Collaborative Review – Prostate Cancer

Pelvic Complications After Prostate Cancer Radiation Therapy and Their Management: An International Collaborative Narrative Review

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Abstract

Context: Radiotherapy used for treating localized prostate cancer is effective at prolonging cancer-specific and overall survival. Still, acute and late pelvic toxicities are a concern, with gastrointestinal (GI) and genitourinary (GU) sequelae being most common as well as other pelvic complications.
Objective: To present a critical review of the literature regarding the incidence and risk factors of pelvic toxicity following primary radiotherapy for prostate cancer and to provide a narrative review regarding its management.
Evidence acquisition: A collaborative narrative review of the literature from 2010 to present was conducted.
Evidence synthesis: Regardless of the modality used, the incidence of acute high-grade pelvic toxicity is low following conventionally fractionated external beam radiotherapy (EBRT). After moderate hypofractionation, the crude cumulative incidences for late grade 3 or higher (G3+) GI and GU complications are as high as 6% and 7%, respectively. After extreme hypofractionation, the 5-yr incidences of G2+ GU and GI toxicities are 3–9% and 0–4%, respectively. Following brachytherapy monotherapy, crude rates of late G3 + GU toxicity range from 6% to 8%, while late GI toxicity is rare. With combination therapy (EBRT and brachytherapy), the cumulative incidence of late GU toxicity is high, between 18% and 31%; however, the prevalence is lower at 4–14%. Whole pelvic radiotherapy remains a controversial treatment option as there is increased G3+ GI toxicity compared with prostate-only treatment, with no overall survival benefit. Proton beam therapy appears to have similar toxicity to photon therapies currently in use. With respect to specific complications, urinary obstruction and urethral stricture are the most common severe urinary toxicities. Rectal and urinary bleeding can be recurrent long-term toxicities. The risk of hip fracture is also increased following prostate radiotherapy. The literature is mixed on the risk of in-field secondary pelvic malignancies following prostate radiotherapy. Urinary and GI fistulas are rare complications. Management of these toxicities may require invasive treatment and reconstructive surgery for refractory and severe symptoms.

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Conclusions: There has been progress in the delivery of radiotherapy, enabling the administration of higher doses with minimal tradeoff in terms of slightly increased or equal toxicity. There is a need to focus future improvements in radiotherapy on sparing critical structures to reduce GU and GI morbidities. While complications such as fistulae, bone toxicity, and secondary malignancy are rare, there is a need for higher-quality studies assessing these outcomes and their management.

Patient summary: In this report, we review the literature regarding pelvic complications following modern primary prostate cancer radiotherapy and their management. Modern radiotherapy technologies have enabled the administration of higher doses with minimal increases in toxicity. Overall, high-grade long-term toxicity following prostate radiotherapy is uncommon. Management of late high-grade pelvic toxicities can be challenging, with patients often requiring invasive therapies for refractory cases.

1. Introduction

The efficacy of radiotherapy for localized prostate cancer is highly related to radiation dose [1]. Current guidelines for radiotherapy in all-risk prostate cancer are summarized in Table 1. Since 2009, several techniques that enable dose escalation, reduce treatment time, and curtail complications have been investigated [2]. These include increasing the total dose with external beam radiation therapy (EBRT), increasing the radiation dose per fraction (moderate and extreme hypofractionation [HP]), and the use of brachytherapy (BT) monotherapy and combination therapy.

Following radiotherapy treatment, there is a risk of pelvic toxicity. The severity of toxicity can be graded using one of several accepted toxicity scales, based on symptoms and interventions (Table 2). When assessing radiotherapy toxicity, it would be ideal to compare studies across modalities; however, there is inconsistency in the literature with regard to dosing, timing and frequency of follow-up, toxicity scales, and treatment strategies [3].

Management of pelvic toxicities can range from conservative to reconstructive surgery depending on severity. With few clinical trials evaluating management strategies, there is minimal consensus on the optimal approach in most scenarios.

This review will describe the incidence and risk factors for pelvic toxicity reported in the contemporary literature following radical primary radiotherapy for all-risk localized prostate cancer. We will also describe the role of medical and surgical strategies for specific pelvic toxicities, focusing on the management of genitourinary (GU) and gastrointestinal (GI) toxicities.

Table 1 – Standard radiotherapy treatment approaches by prostate cancer risk

Prostate cancer risk	Modality	Fractionation	Dose/fraction (Gy)	Total dose (Gy)	Guideline
Low Risk					
	EBRT	Conventional fractionation	1.8–2	76–80	ASCO/CCO 2017 [25], ACR appropriateness criteria [4]
		Moderate hypofractionation	2.1–3.5	52–73	AUA/ASTRO/SUO 2017 [116]
		Extreme hypofractionation (SBRT)	3.5–15		ACR appropriateness criteria [4]
	LDR BT monotherapy		–	115–145	ASCO/CCO 2017 [25]
Intermediate risk					
Favorable (low)-intermediate	HDR BT monotherapy LDR BT monotherapy		8.5–13	26–38 115–145	ASCO/CCO 2017 [25], GEC/ESTRO 2013 [26] NCCN 2018 [117]
Unfavorable (high)-intermediate	EBRT + HDR BT boost ± ADT EBRT + LDR BT boost ± ADT		EBRT: 1.8–2.75(HDR) 1.8–2.0 (LDR) HDR BT: 5–15	EBRT: 35.7–46 (HDR) 45–50.4 (LDR) HDR BT: 11–22 LDR BT 85–115	ASCO/CCO 2017 [25], GEC/ESTRO 2013 [26] NCCN 2018 [117]
High risk					
	EBRT + HDR BT boost + ADT EBRT + LDR BT boost +ADT		EBRT: 1.8–2.75 (HDR) 1.8–2.0 (LDR) HDR BT: 5–15	EBRT: 35.7–46 (HDR) 45–50.4 (LDR) HDR BT: 11–22 LDR BT 85–115	ASCO/CCO 2017 [25] NCCN 2018 [117]

ACR = American College of Radiology; ADT = androgen deprivation therapy; ASCO = American Society of Clinical Oncology; ASTRO = American Society for Radiation Oncology; AUA = American Urological Association; BT = brachytherapy; CCO = Cancer Care Ontario; EBRT = external beam radiation therapy; ESTRO = European Society for Radiotherapy and Oncology; GEC = Groupe Européen de Curiethérapie; HDR = high-density rate; LDR = low-density rate; NCCN = National Comprehensive Cancer Network; SBRT = stereotactic body radiation therapy; SUO = Society of Urologic Oncology.

Table 2 – Gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) morbidity scale and the Common Terminology Criteria for Adverse Events (CTCAE) v4.03

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastrointestinal					
RTOG/EORTC acute	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (eg, Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion	Death
RTOG/EORTC late	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula	Death
CTCAE V4.03					
Rectal bleeding	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (eg, altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Genitourinary (bladder)					
RTOG/EORTC acute	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour; dysuria, urgency, bladder spasm requiring local anesthetic (eg, Pyridium)	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis	Death
RTOG/EORTC late	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency and dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity <100 cc); severe hemorrhagic cystitis	Death
CTCAE V4.03					
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective endoscopic, radiologic, or operative intervention indicated; limiting self-care	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Urinary Fistula	–	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self-care; elective radiologic, endoscopic, or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary, or suprapubic catheter indicated	Symptomatic and altered organ function (eg, hydronephrosis or renal dysfunction); elective radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

ADL = activities of daily living; GI = gastrointestinal; IV = intravenous; TPN = total parenteral nutrition.

2. Evidence acquisition

We systematically searched Medline and Embase from 2010 to present (January 8, 2018) using a variety of terms covering prostate cancer, radiation therapy, toxicity and adverse effects, toxicity grading scales, and specific known pelvic complications of prostate cancer radiotherapy (see the Supplementary material). We considered large observational studies, prospective trials, and systematic reviews assessing all types of photon and proton external therapies and BT for primary radical radiation therapy to the prostate. We excluded studies on salvage treatments, as it would be difficult to isolate the toxicity of radiotherapy from that of surgery. We excluded clinical trials reporting only quality of life or patient-reported outcomes. We also searched Medline and Embase databases for studies on the management of pelvic toxicities following prostate cancer treatment, using terms describing known specific complications (cystitis, proctitis, urinary obstruction, urethral and ureteral stricture, rectourethral fistula [RUF], pubic symphyseal fistula) along with the terms "treatment," "therapy," or "management." We then performed a manual search through reference lists for additional sources. The lead author then compiled a proposed bibliography and outline that was iteratively revised by all coauthors. Once the structure of the review was agreed upon, the first and senior authors drafted this narrative review, which was critically revised by all coauthors. The final review represents the consensus of the authors.

3. Evidence synthesis

3.1. GU and GI complications following prostate radiotherapy

3.1.1. Toxicity following conventional fractionation EBRT

Conventionally fractionated, dose-escalated EBRT (1.8–2.0-Gy fractions, delivered in approximately 15 min/d, 5 d/wk, for 8–9 wk, to a total dose of 76–80 Gy) is an accepted treatment approach for men in all disease risk groups [4]. Table 3 summarizes the incidence of GU and GI toxicities reported from contemporary randomized clinical trials using conventionally fractionated EBRT.

Acute severe GU toxicity (<3 mo, grade 3 or worse) following conventional fractionation is limited [5,6]. However, late toxicity following conventional fractionation can be significant. The cumulative incidence of late toxicity in the Dutch dose escalation trial when comparing 70 versus 80 Gy [7] was 10–14% for late G2+ gross hematuria and 6–9% for late urinary obstruction. GI late toxicity was also significant, with 14–20% of patients experiencing G2+ rectal toxicity and 19–28% experiencing rectal bleeding. In the largest conventional fractionation dose escalation trial, the 5-yr cumulative incidence of late G2+ GU toxic effects was increased for the dose escalation arm (79.2 Gy) to 12% compared with 7% following the standard dose (70.2 Gy) [5].

When comparing radiotherapy delivered using intensity-modulated radiotherapy (IMRT) with three-dimensional conformal radiotherapy (3DCRT), patients experienced decreased rates of acute and late G2+ GI toxicity [8,9]. In a meta-analysis of 23 studies, there was no difference in terms of late GU toxicity, while IMRT slightly increased acute G2+ GU complications [8]. More recent trials have shown reduced GU toxicity with IMRT [9,10].

GI toxicity following conventionally fractionated EBRT can be moderated. In a phase III study of men undergoing dose-escalated IMRT to 79.2 Gy with magnetic resonance imaging planning, the use of hydrogel spacer reduced the risk of late G2+ GI toxicity from 6% to 0% [11].

3.1.2. Toxicity following moderate hypofractionation using EBRT

Owing to the low α/β value for prostate cancer [12], hypofractionation theoretically can improve cancer control without increasing toxicity to normal tissue and it can be implemented over a shorter period of time, improving radiotherapy convenience and expense [13]. Moderately

Table 3 – Trials reporting early and late genitourinary and gastrointestinal toxicity after conventional fractionation external beam radiotherapy

Authors	Type of study	N	Modality	Dose (Gy)	Fx	FU	Acute toxicity		Late toxicity		LOE	Scale
							Acute GU	Acute GI	Late GU	Late GI		
Beckendorf et al. (2011) [7]	Phase III multicenter	153	3DCRT	70		5.1	NR	NR	G3/4: 3% (4/153)[a]	G3: 2% (3/153) G4: 0[b]	1b	RTOG and LENT-SOMA
		153	3DCRT	80		5.1	NR	NR	G3/4: 2% (3/153)	G3: 6% (9/153) G4: 0	1b	RTOG and LENT-SOMA
Michalski et al. (2010) [41]	Phase I/II multicenter	75	3DCRT	68.4		10.3	NR	NR	G3/4: 19–24%[c]	G3/4: 9–13%	1b	RTOG
		97	3DCRT	73.8		9.9	NR	NR	G3/4: 16–22%[c]	G3/4: 7–9%[c]	1b	RTOG
		103	3DCRT	79.2		9.2	NR	NR	G3/4: 18–21%[c]	G3/4: 11–14%[c]	1b	RTOG
		115	3DCRT	74.0 (2 Gy/fx)		7.7	NR	NR	G3/4: 21–29%[c]	G3/4: 10–16%[c]	1b	RTOG
		118	3DCRT	78 (2 Gy/fx)		6.1	NR	NR	G3/4: 23–28%[c]	G3/4: 25–26%[c]	1b	RTOG
Michalski et al. (2013) [6]	Phase III multicenter	751	3DCRT (502) IMRT (249)	70.2	39	8.4	G3: 1% (10) G4: 0	G3: <1% (2) G4: 0	G3: 2% (15) G4: 0	G3: 3% (23) G4: 0	1b	CTCAE 3.0
Michalski et al. (2018) [5] RTOG 0126		748	3DCRT (491) IMRT (257)	79.2	44	8.4	G3: 1% (10) G4: 0	G3: <1% (2) G4: 0	G3: 3% (19) G4: <1% (3)	G3: 5% (34) G4: <1 (3)	1b	CTCAE 3.0

CTCAE 3.0 = Common Terminology Criteria for Adverse Events version 3.0; 3DCRT = three-dimensional conformal radiation therapy; FU = follow-up (median, years); Fx = fractions; G = grade; GI = gastrointestinal; GU = genitourinary; IMRT = intensity-modulated radiation therapy; LENT-SOMA = Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scale; LOE = level of evidence; NR = not reported; RTOG = Radiation Therapy Oncology Group.
Yellow highlighted rows represent dose escalation arms within the trial.
[a] The incidence of late hematuria was 10–14%, and late urinary obstruction was 6–9%.
[b] The incidence of late rectal bleeding was 19–28%.
[c] Late toxicity was counted after 120 d due to prolonged treatment.

Table 4 – Hypofractionation trials reporting early and late genitourinary and gastrointestinal toxicity after external beam radiotherapy

Authors	Type of study	N	Modality	Dose (Gy)	Fx	FU	ADT	Acute toxicity		Late toxicity		LOE	Scale
								Acute GU	Acute GI	Late GU	Late GI		
Arcangeli et al. (2011) [118] Arcangeli et al. (2017) [119]	Phase III single center	85	3DCRT	80	40	2.9	100%	G3: 1.2% (1/85) G4: 0	G3: 0 G4: 0	G3: 2.4% (2/85) G4: 0	G3: 0 G4: 0	1b	Acute: RTOG Late: LENT-SOMA
		83	3DCRT	62	20	2.7	100%	G3: 1.2% (1/83) G4: 0	G3: 0 G4: 0	G3: 0 G4: 1.2% (2/83)	G3: 1.2% (1/83) G4: 0	1b	
Wu et al. (2012) [120]	Phase II multicenter	73	3DCRT & VMAT	55	16	4.6	15%	G3: 3% (2/73) G4: 0	G3: 4% (3/73) G4: 0	G3: 6.8% (5/73) G4: 0[a]	G3: 4% (3/73) G4: 0[b]	1b	RTOG
Menkarios et al. (2011) [121] Zimmerman et al. (2016) [122]	Phase II multicenter	80	3DCRT	45	9	6.9	0%	G3: 4% (4/80) G4: 0	G3:0 G4:0	G3: 2.5% (2/80) G4: 1.3% (1/80)[d]	G3: 12.5% (10/80)[c] G4: 0	1b	RTOG
Lee et al. (2016) [15] (RTOG 0415)	Phase III multicenter	542	3DCRT or IMRT	73.8	41	5.8	0%	G3: 2.4% (13/542) G4: 0	G3: <1% (3/542) G4: 0	G3: 2.1% (11/542) G4: <1% (1/542)	G3: 2.4% (13/542) G4: <1% (1/542)	1b	CTCAE 3.0
		550	3DCRT or IMRT	70	28	5.8	0%	G3: 3.3% (18/550) G4: 0	G3: <1% (3/550) G4: <1% (1/550)	G3: 3.5% (19/550) G4: 0	G3: 4.0% (22/550) G4: 0	1b	
Aluwini et al. (2015) [16] Aluwini et al. (2016) [123] (HYPRO)	Phase III multicenter	392	IMRT & 3DCRT	78	39	5	67%	G3: 18% (69) G4: 1% (2)	G3: 5% (18) G4: 0	G3+: 12.9% (CI 9.7–16.7) G4: <1% (3)[h]	G3+: 2.6% (CI 1.2–4.7)[e,f]	1b	RTOG
		403	IMRT & 3DCRT	64.6	19	5	67%	G3: 20% (82) G4: <1% (2)	G3: 6% (23) G4:0	G3+: 19.0% (CI 15.2–23.2) G4: <1% (2)[e]	G3+: 3.3% (CI 1.7–5.6)[e,f]	1b	
Dearnaley et al. (2016) [14] (CHHiP)	Phase III multicenter	1065	IMRT	74	37	5.2	97%	G2+: 46% (331/715)[g]	G2+: 25% (176/715)[g]	G2+: 9.1% (66) G3+: 2% (17)[e]	G2+: 13.7% (111) G3+: 3% (27)[h]	1b	RTOG
		1074	IMRT	60	20	5.2	97%	G2+: 49% (356/720)[g]	G2+: 38% (277/720)[g]	G2+: 11.7% (88) G3+: 3% (20)[h]	G2+: 11.9% (105) G3+: 6% (38)[h]	1b	
		1077	IMRT	57	19	5.2	97%	G2+: 46% (327/713)[g]	G2+: 38% (270/713)[g]	G2+: 6.6% (57) G3+: 4% (23)[h]	G2+: 11.3% (95) G3+: 3% (21)[h]	1b	
Catton et al. (2017) [17] (PROFIT)	Phase III multicenter	598	IMRT& 3DCRT	78	39		0%	G3: 4.0% (24/598) G4: 0	G3: 0.5% (3/598) G4: 0	G3: 2.8% (17/598) G4: 0.2% (1/598)	G3: 2.7% (16/598) G4: 0.2% (1/598)	1b	RTOG
		608	IMRT& 3DCRT	60	20		0%	G3: 3.9% (24/608) G4: 0	G3: 0.7% (4/608) G4: 0	G3: 2.0% (12/608) G4: 0.2% (1/608)	G3: 1.5% (9/598) G4: 0	1b	
Hoffman et al. (2014) [124]	Phase III single center	101	IMRT & IGRT	75.6	42	6	23%	–	–	G3: 1% (1) G4: [i]	G3: 1% (1) G4: [i]	1b	RTOG
		102	IMRT & IGRT	72	30	6	25%	–	–	G3: 0 G4: [i]	G3: 2% (2) G4: [i]	1b	
Pollack et al. (2013) [125]	Phase III single center	151	IMRT	76	38	5.7	47%	–	–	G3+: 3.3% G4: 0	G3+: 2% G4: 0	1b	Modified RTOG
		152	IMRT	70.2	26	5.7	45%	–	–	G3+: 4% G4: 0	G3+: 2% G4: 0	1b	

ADT = androgen deprivation therapy (patients receiving); CI = confidence interval; CTCAE 3.0 = Common Terminology Criteria for Adverse Events version 3.0; 3DCRT = three-dimensional conformal radiation therapy; FU = follow-up (median, years); Fx = fractions; G = grade; GI = gastrointestinal; GU = genitourinary; HF = hypofractionation; IGRT = image-guided radiation therapy; IMRT = intensity-modulated radiation therapy; LENT-SOMA = Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scale; LOE = level of evidence; RTOG = Radiation Therapy Oncology Group; SF = standard fractionation; TURP = transurethral resection of the prostate; VMAT = volumetric modulated arc therapy.
Yellow highlighted rows indicate groups that received hypofractionated radiotherapy.
[a] Late GU: three transient events (evaluation cystoscopy, cauterization, TURP), one incontinence at 24 mo, one hematuria requiring transfusion.
[b] Late GI: all patients experienced rectal bleeding.
[c] Late GI: eight patients received argon beam coagulation, one patient discontinued oral anticoagulation, and one patient received conservative treatment.
[d] Late GU: G3—severe frequency and dysuria; G4—intractable hematuria requiring cystectomy.
[e] Estimated cumulative incidences, rather than crude, were reported for late toxicity.
[f] Interventional anticoagulation (proctoscopy/colonoscopy): SF 2% (9/387), HF 3% (12/395).
[g] Acute toxicity reported as peak proportions at 4–8 wk.
[h] Late toxicity reported as cumulative incidence at 5 yr.
[i] Crude cumulative incidence.

hypofractionated radiotherapy is a standard for EBRT primary treatment of prostate cancer, delivered in 2.1–3.5 Gy/fraction for approximately 15 min/d, 5 d/wk, for about 4 wk, to a total dose of ~52–72 Gy. Trials reporting toxicities following hypofractionated EBRT are summarized in Table 4.

In the largest hypofractionation trial reported to date (CHHiP) [14], there were no differences in high-grade GU and GI toxicities with hypofractionation compared with standard fractionation. They found that acute G2+ bladder toxicity occurred in 46–49% of patients across groups. At 5 yr, G3+ bladder events occurred in 1% of patients. This trial demonstrated more favorable bladder toxicity results compared with other phase III studies assessing hypofractionation (RTOG 0415 [15], HYPRO [16], and PROFIT [17]), which was likely a result of the lower total delivered dose, relatively narrow planning target volume margins, and normal tissue dose constraints.

3.1.3. Toxicity following extreme hypofractionation using EBRT

Extreme hypofractionation, otherwise known as stereotactic body radiation therapy (SBRT), refers to treatment utilizing a precise position within a 3D space and consisting of five or fewer treatments [18]. In prostate radiotherapy, it is delivered using ≥6.5 Gy daily doses. SBRT is being offered more frequently, particularly for low-risk disease in men who desire treatment. Several phase II trials have been reported and long-term toxicity results are promising, with 5-yr incidences of 3–9% for G2+ GU toxicity and 0–4% for G2 + GI toxicity [19–21]. Widmark et al. [22] have reported on long-term results of a single-phase III trial comparing standard fractionation EBRT (39 fractions, 78 Gy total) with SBRT (seven fractions, 42.7 Gy total), with no significant differences in late G2+ GU and GI toxicities.

In addition to prospective trials, long-term SBRT toxicities have been investigated using administrative databases. Yu et al. [23] compared SBRT versus IMRT using a national sample of Medicare beneficiaries aged ≥66 yr. By 6 mo, 16% of patients who had received SBRT had a treatment-related GU toxicity versus 13% of IMRT patients, and this risk persisted for 24 mo. There was also an increased risk of specific GU procedures, including diagnostic and corrective procedures from 6 to 24 mo after SBRT compared with IMRT. Halpern et al. [24] found a similarly increased risk of GU toxicity when comparing SBRT with IMRT, BT, and 3DCRT. The disparity between prospective trial results and real-world data likely represents both the lack of toxicity grading within administrative databases and the variability in general practice of SBRT platforms and physician and center experience, given the technical complexity of SBRT.

3.1.4. Toxicity following BT monotherapy

BT monotherapy delivered at a low-dose rate (LDR) is recommended as a treatment for favorable and unfavorable intermediate-risk prostate cancer [25,26], although several groups have studied high-dose rate (HDR) BT as monotherapy [27–29]. LDR refers to permanently implanted radioactive seeds, often with iodine-125 (I^{125}), delivering a dose rate between 0.3 and 2.0 Gy/h, for a total dose of 115–145 Gy.

There are no randomized trials reporting on toxicity following LDR BT monotherapy for localized prostate cancer. From large institutional series, crude overall rates of long-term G3 GU+ toxicity range from 6% to 8% [30,31]. Long-term G3+ GI toxicity is rare [31]. In the British Columbia Cancer Center LDR BT series, with a prescribed dose of 144 Gy to the planning target volume, the acute G3+ GU toxicity is 8% overall, although it ranges from 16% in their initial 500-person cohort to 3% in their final cohort, suggesting improvement in toxicity with experience [32].

3.1.5. Toxicity following combination therapy (BT and EBRT)

The Cancer Care Ontario/American Society for Clinical Oncology guidelines on BT recommend BT boost (LDR or HDR) in addition to EBRT for unfavorable intermediate- and high-risk patients [25]. Combination therapy results in improved biochemical recurrence–free survival in high-risk prostate cancer compared with dose-escalated EBRT [33]. The largest combination therapy trial, ASCENDE-RT, which treated patients with a combination of EBRT and 46 Gy followed by an I^{125} LDR boost [34], found the cumulative incidence of late G3+ GU toxicity to be 18% in the BT arm, with approximately half being urethral strictures, compared with 5% in the EBRT arm (78 Gy). Most of the complications were transient, as the prevalence of G3+ GU toxicity at 5 yr reduced to 9% in the combination arm. Similarly, in the second largest trial [35], which randomized patients to receive EBRT of 55 Gy or combination EBRT (35.75 Gy in 13 fractions) followed by an HDR BT boost of 17 Gy, the cumulative incidence of G3+ GU toxicity at 7 yr was 31%, with prevalence rates of 4–14%.

3.1.6. Toxicity following whole pelvis radiotherapy

The benefit of elective whole pelvis radiotherapy (WPRT) of the pelvic nodal regions in clinically node-negative intermediate- to high-risk prostate cancer patients remains controversial, as no improvement in overall survival was reported in randomized trials comparing WPRT with prostate-only radiotherapy (PORT) [36,37].

In the RTOG 94-13 trial [36], there was no significant difference in acute G3+ GI and GU toxicities among the four arms of the study (WPRT vs PORT with either neoadjuvant androgen deprivation therapy [ADT] or adjuvant ADT). In an update of this trial, GU toxicity was the most common late G3+ toxicity; however, there was no difference between treatments (6% in WPRT vs 5% in PORT). For late G3+ GI toxicity, the cumulative incidence was highest for patients in the WPRT (plus neoadjuvant ADT) group (7% at 10 yr) and lowest for those in the PORT (plus neoadjuvant ADT) group (1%).

Since the earlier WPRT trials used 3DCRT, which has now been largely supplanted by IMRT, NRG/RTOG 0924 [38] will evaluate whether WPRT delivered using IMRT combined with a dose-escalated prostate boost will improve survival without increasing GI toxicity.

3.1.7. Toxicity following proton beam therapy

Although the use of proton beam therapy (PBT) has grown exponentially over the present decade, its availability remains limited in many healthcare systems, mostly owing to a lack of mature phase III data and significant cost [39].

In the most recently reported phase III study, Zietman et al. [40] reported 10-yr follow-up of patients receiving PBT for dose escalation, with either 19.8 Gy equivalents (GyE) or 28.8 GyE, in either 11 or 16 1.8-GyE fractions in addition to 50.4 Gy delivered with photons. Only 2% of patients in both arms experienced late G3+ GU toxicity and 1% experienced late G3+ GI toxicity, which is comparable with other photon dose escalation trials [7,41]. Similarly, a more recent prospective study of 1327 men receiving PBT at 78 GyE demonstrated that the actuarial 5-yr rates of late G3+ GI and GU toxicities were 0.6% and 2.9% [42], respectively.

In comparison with photon therapies, we know from population-level studies that patients receiving PBT appear to have similar rates of morbidity to those receiving IMRT [43], except for increased late GI toxicity in PBT patients

[44,45]. There is however a need for prospective studies, such as the ongoing PARTIQoL [46] and COMPPARE [47] trials, that compare PBT and IMRT in a standardized fashion.

3.2. Specific pelvic complications following prostate cancer radiation therapy and their management

3.2.1. Urinary obstruction and urethral stricture

In a randomized dose escalation trial of 3DCRT, 3% of men developed obstruction within 2 yr with an additional 3% beyond 2 yr [48]. Risk factors for early obstruction (<2 yr) included previous transurethral resection of the prostate (TURP), lower urinary tract symptoms (nocturia and incontinence), a dose to the seminal vesicles of >10 Gy, and high-dose regions on the bladder [49]. With combination therapy, using 3DCRT (45 Gy in daily 1.8 Gy doses) and HDR BT (19 Gy in two fractions), urinary retention represents 25% of acute and 4% of late G2+ GU complications [50]. In population-based data from the USA, bladder outlet obstruction is the most common urinary adverse event following prostate radiotherapy, with event rates of 18 and 31 per 1000 person years following EBRT and combination therapy, respectively [51]. In Canada, the risk of admission to hospital for urinary obstruction after any radiotherapy for prostate cancer was 9.4 events per 1000 person years [52].

Acute urinary obstruction secondary to radiotherapy is often managed expectantly with catheterization and medical therapy. Channel TURP due to urinary retention or refractory voiding symptoms is also performed, although the risk of urinary incontinence is increased [53]. Late urinary obstruction can be managed similarly.

The incidence of radiation-induced urethral strictures varies between 0% and 18% [54]. In a review of over 16 000 patients, the prevalence of strictures was 2% after EBRT, 2% after BT, and 5% after combination therapy [55]. With combination therapy, the incidence is 14% at 48 mo [56]. Severe urethral toxicity has been reported in other HDR BT series, with 12% of patients experiencing urethral strictures requiring operative intervention at 5 yr, compared with 0.3% in a matched cohort of EBRT patients from the same institution [57]. Long-term incidence estimates for urethral strictures requiring operative intervention were lower in the second largest randomized trial of combination therapy, at 6% and 8% at 5 and 7 yr, respectively [35]. Population-based estimates for urethral dilation or incision for stricture was 5.1 events per 1000 person years [52].

The major radiation risk factors for urethral stenosis following primary therapy include the use of combination therapy [55] and the delivery of a high dose to the prostatic apex [58]. Patient factors include a history of TURP and hypertension [59].

Management of postradiation urethral strictures is challenging due to radiation effects such as endarteritis, hypovascularity, and interstitial fibrosis. The general approach requires consideration of stricture location, tissue viability, and sphincter competence. Postradiation strictures are initially managed by dilation and/or visual internal urethrotomy, although recurrence is common. Beyond endoscopic management, short strictures (≤2 cm) of the mid to proximal bulbar urethra are amenable to excision and primary anastomosis, while strictures with a membranous component require maneuvers including urethral dissection and splitting the corporal bodies to gain additional length. For longer strictures, substitution is used with either flap or graft [60–62]. Overall success rates for open urethroplasty range from 70% to 90% in several case series [58,60–62], although these come from specialist centers with short follow-up. Moreover, success is often defined as the absence of obstructive voiding symptoms and/or further urethral interventions, which may overestimate the success rate.

3.2.2. Macroscopic hematuria

Gross hematuria can be a recurring toxicity of prostate radiotherapy, with 5- and 10-yr incidence rates of 5% and 8%, respectively [63]. In the HYPRO hypofractionation trial, the 8-yr actuarial rates of gross hematuria was 18% [64] when they disregarded cancer-related events and 32% of patients experienced three or more episodes. Known treatment risk factors for radiation hemorrhagic cystitis include the relative volume of bladder receiving ≥40 Gy [64][4] and external beam radiation in combination with BT [65]. Patient factors include a prostate volume of >40 cm^3 and anticoagulation therapy [63,66].

Management of gross hematuria secondary to radiotherapy progresses in a sequential manner, consisting of resuscitation and reversal of anticoagulation as appropriate, clot evacuation, and bladder irrigation as well as supportive therapy. The evidence for systemic therapies is of low quality [67], and they would not suffice for G2+ cystitis. However, there is reasonable evidence for the use of hyperbaric oxygen (HBO). HBO promotes healing in the bladder through capillary angiogenesis [68]. HBO therapy after an episode of gross hematuria results in an improvement in symptom scores [69] and complete resolution of hematuria in the majority of cases [70,71]. The typical treatment regimen, however, is time consuming, requiring 30–60 dives at 2.0 atmospheric absolute pressure for 90–120 min per dive [69–71]. For G3+ cystitis, if the bleeding is intractable, ablation targeting the bladder mucosa is attempted, using electrocoagulation, argon beam, or laser [72]. This can be followed by intravesical therapy. The principles behind using intravesical treatments include sterilization, lavage, and arrest of focal bleeding. Small case series on intravesical formalin, in formulations of 2–4%, demonstrate that it can achieve complete response relatively quickly [73], lasting for several months [67], although it is toxic at higher concentrations. Alum, an aluminum salt, is also used to control capillary bleeding in mild cases, although in heavy bleeding it may lead to clotting, retention, and further bleeding. In patients with bleeding that is significant enough to require cystoscopy and clot evacuation, response to a single procedure is reasonable, with 61% response in a case series of 33 patients [74]. More recently, sodium hyaluronate has been administered with the intention of replenishing the glycosamine glycan layer of the bladder, demonstrating equal effectiveness to HBO in ameliorating bleeding [75].

In refractory cases, cystectomy and urinary diversion are the last resort, often with a significant risk of high-grade complications and mortality [76].

3.2.3. Rectal bleeding

Rectal bleeding or RTOG G2+ late rectal toxicity is often considered a toxicity endpoint in radiotherapy trials. Of the late GI toxicities, GI bleeding/ulceration is most common, with the rectal bleeding rate in one claims-based study being highest for IMRT (8.3 events/1000 person years), followed by 3DCRT (7.8), combination treatment (6.3), and BT monotherapy (4.4) [45]. It should be noted that observational studies are confounded by the fact that IMRT was generally delivered at a higher dose then 3DCRT. Five-year cumulative incidences of rectal bleeding from two Dutch randomized controlled trials of IMRT and 3DCRT with doses of 78 Gy were 4% and 6%, respectively [77]. Following BT, either alone or in combination with EBRT, large institutional cohorts demonstrate an actuarial risk of 6% for G2+ rectal bleeding, with only 1% of all patients requiring intervention [78].

Previously established risk factors for rectal bleeding following radiotherapy include increasing age, anticoagulant use [79], an increased volume of rectum receiving doses $\geq$60 Gy [80], and undergoing abdominal surgery before radiotherapy (excluding prostatectomy) [81], and for those patients who have received previous surgery, a rectal volume receiving $>$70 Gy was an important dosimetric factor for predicting late rectal bleeding [79,82].

Management of hemorrhagic radiation proctitis follows a similar course to radiation cystitis. Systemic and topical therapies are used for lower-grade toxicity. Metronidazole has the best evidence for its use orally, combined with ciprofloxacin [83] when compared with formalin instillation. Other oral agents have mixed results [84]. Formalin instillation therapy is also effective [85], typically at 4% concentration [86], although older studies report a small proportion of patients having significant complications including stricture, postprocedural pain, and rectosigmoidal necrosis [87]. As such, it is suitable for rectal bleeding that is refractory to less toxic endoscopic therapy. Sucralfate, a sulfated polyanionic disaccharide, used as an oral preparation following argon plasma coagulation (APC), failed to show a benefit to bleeding control [88]. Sucralfate enemas self-administered twice daily have shown improvement in symptoms for the majority of patients with occasional complete resolution [89]. HBO therapy can also be effective in managing refractory rectal bleeding, with one multicenter randomized trial demonstrating significant improvement in toxicity and quality of life scores over treatment with air at 1.1 atmospheric pressure [90], although there is more recent conflicting evidence [91].

Endoscopic therapy is employed in cases refractory to medical therapy. APC is the most commonly studied of the endoscopic modalities [92]. APC is equally as effective as bipolar electrocoagulation [93] and formalin instillation [94] in the treatment of intractable rectal bleeding. However, it has limited efficacy for severe and widespread proctitis [95]. Other endoscopic energy modalities have largely been supplanted by APC.

Surgery is often the last resort for refractory bleeding, or when strictures develop leading to obstruction or sepsis. There is no preferred surgical approach as data are limited to institutional case series. Surgery can involve a defunctioning loop colostomy [96], a Hartmann's procedure, a resection, and an anastomosis or pull-through procedure. Much like urinary diversion in this population, the morbidity and mortality rates after diversion and resection are approximately 21–27% and 4–7%, respectively [97].

3.2.4. Ureteral strictures

Obstruction of the pelvic ureter following primary prostate radiotherapy is a rare event, with a 10-yr cumulative incidence of 1–2% following BT and EBRT, respectively [51]. Nam et al. [52] found that open ureteric reimplant occurred at a rate of 0.1 events per 1000 person years following all prostate radiotherapy compared with none after radical prostatectomy. Ureteric obstruction most commonly occurs following salvage radiotherapy [51], likely owing to the more medial and inferior position of the distal ureters following prostatectomy [98]. Ureteric obstruction can be managed initially with stenting and periodic stent exchanges. After evaluating bladder capacity to ensure that it is sufficient, ureteric reimplantation is an option, with standard maneuvers such as creation of a Boari flap for longer distal strictures. The use of an omental flap to supplement the blood supply near the anastomosis is described [99]. If bladder capacity is small, urinary diversion can be pursued.

3.2.5. Rectourethral fistulas

RUFs from primary prostate cancer therapy are increasing in prevalence, with radiation now accounting for 50% of RUFs since 1998 [100]. GI fistulas are still rare however, occurring at a rate of 0.3 events/1000 person years after EBRT according to the Surveillance, Epidemiology, and End Results (SEER)-Medicare population data [45]. After BT, the crude incidence of RUFs is 0.26–0.32% [101,102] with median time to fistulization of 25–32 mo.

A multidisciplinary approach (colorectal surgery, urology, and other specialties as needed) should be employed in the diagnostic workup and management of RUFs [103]. Diagnostic workup consists of cystoscopy and urethrogram to assess the morphology of the fistula, look for strictures, and determine bladder capacity. Investigation of the GI tract is recommended to rule out stricture or another primary malignancy. If a pelvic collection is suspected, then cross axial imaging is warranted. Although radiotherapy-induced RUFs are rarely simple [104], initial management for simple fistulas includes urinary catheterization for up to 12 wk [105]. Such conservative management is pursued for patients who wish to defer surgical management and can consist of bladder drainage via catheterization with regular changes, fecal diversion with an end colostomy, and antibiotic prophylaxis [105]. Keller et al. [103] describe a treatment algorithm for complex RUFs, where patients with severe symptoms, fistula size $\geq$1 cm, significant tissue scarring from radiotherapy, severe urethral stricture, and/or pelvic sepsis undergo diverting stoma, which has been

adopted in other series [106]. Mundy and Andrich [104] have questioned the need for fecal diversion in this setting, as it is unlikely to cause spontaneous healing and is not necessary for subsequent surgical repair. Although there are several options for RUF surgical repair, after radiation the transabdominal approach is most frequently used, followed by the transphincteric and transperineal approaches [100,104]. All approaches employ interposition or advancement flaps in the repair, with the goal of supplementing the poor intrinsic blood supply by interposing vascularized tissue.

3.2.6. *Pelvic bone complications of prostate radiotherapy*

Bone complications following prostate cancer radiotherapy are uncommon. Zelefsky et al. [107] reported a 3% incidence of moderate-to-severe hip pain at median time of 72 mo following EBRT (64.8–86.4 Gy in 1.8 Gy fractions). They found that prolonged salvage ADT and degenerative joint disease were independent risk factors. Elliott et al. [108] found that 8% of men who received EBRT alone experienced hip fracture at 10 yr and they were at 76% increased risk compared with men managed with surgery [108]. Although ADT is a known risk factor for fall-related fractures, only 9% of men experienced hip fracture after EBRT + ADT compared with 8% after EBRT alone, likely owing to the short course of ADT.

Another bone-related toxicity, chronic pubic pain, attributed to osteitis pubis, pubic symphysis osteomyelitis [109], or urosymphyseal fistulization [110], is increasingly being recognized as a significant, albeit rare, bone-related pelvic complication associated with prostate cancer treatment. Often patients present after radiation and subsequent bladder neck or transurethral resection therapy [110], and they may also present with concurrent RUFs that extended anteriorly and involved the symphysis pubis [109] or other concurrent complications of treatment. Radiation-induced urosymphyseal fistulization is managed initially via catheterization, with antibiotics, although this is rarely successful [109]. For those in whom conservative management fails, an abdominoperineal approach is undertaken with the excision of the fistulous tract, debridement of infected pubic bone [109,111], drainage of any cavities, and omentoplasty. The majority also require urinary diversion [109,110].

3.2.7. *Secondary pelvic malignancy risk following prostate radiotherapy*

Determining the risk of secondary pelvic malignancy following prostate cancer radiotherapy has been proved to be difficult due to several factors: long lag time, insufficient power in institutional databases to detect differences, lack of comparator populations, and lack of details regarding radiotherapy modalities in large database studies. A recent systematic review identified that there is a need for high-quality studies [112].

Huang et al. [113] found no significant increase in in-field secondary malignancy risk compared with prostatectomy. de Gonzalez et al. [114] found that the relative risk of bladder cancer was 1.16 (95% confidence interval [CI] 0.95–1.40) and that of rectal cancer was 0.59 (95% CI 0.4–0.88). When comparing BT with EBRT, they found that the risk was lower for all in-field cancers (bladder and rectal) with BT; however, when combining BT with EBRT, the relative risk of bladder cancer was 1.25 (95% CI 1.00–1.56) compared with EBRT alone. Zelefsky et al. [115] reported on patients treated with IMRT (using a median prescribed dose of 81 Gy), and with BT alone or in combination therapy. They found that 15% of EBRT patients and 10% of BT patients developed in-field and out-of-field secondary malignancies after a mean follow up of 84–90 mo. However, compared with a population-matched cohort derived from the SEER tumor registry, they found that there was no excess risk of in-field malignancy.

4. Conclusions

With the uptake of extreme hypofractionation and combination therapy for high-risk prostate cancer, there appears to be a shift from GI toxicity toward GU toxicity. Future work should focus on sparing critical GU structures, such as the bladder neck and urethra. Fistulization, bone toxicity, and secondary malignancy are rare following prostate radiotherapy, but it is necessary to identify modifiable risk factors. There is also a need for higher-quality evidence supporting the management of the various pelvic toxicities following prostate radiotherapy.

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Study concept and design: Matta, Nam.
Acquisition of data: Matta, Chapple, Fisch, Heidenreich, Herschorn, Kodama, Koontz, Murphy, Nguyen, Nam.
Analysis and interpretation of data: Matta, Chapple, Fisch, Heidenreich, Herschorn, Kodama, Koontz, Murphy, Nguyen, Nam.
Drafting of the manuscript: Matta, Nam.
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Appendix A. Supplementary data

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