Should inflammatory bowel disease be a contraindication to radiation therapy: a systematic review of acute and late toxicities

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Literature Review

Abstract

Background: Inflammatory bowel disease (IBD) [i.e., Crohn's disease (CD) and ulcerative colitis (UC)] has been considered a relative contraindication for radiation therapy (RT) to the abdomen or pelvis, potentially preventing patients with a diagnosis of IBD from receiving definitive therapy for their malignancy.

Method: Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) conventions, a PubMed/MEDLINE literature search was conducted using the keywords RT, brachytherapy, inflammatory bowel disease, Crohn's disease, ulcerative colitis and toxicity.

Results: A total of 1,206 publications were screened with an addition of 8 studies identified through hand searching. Nineteen studies met the inclusion criteria for quantitative analysis. The total population across all studies was 497 patients, 50·5% having UC, 37% having CD and an additional 12·5% having unspecified IBD. Primary gastrointestinal malignancy (55%) followed by prostate cancer (40%) composed the bulk of the population. Acute and late grade 3 or greater gastrointestinal specific toxicity ranged from 0–23% to 0–13% respectively for those patients with IBD treated with RT to the abdomen or pelvis. In the literature reviewed, RT does not appear to increase fistula or stricture formation or IBD flares; however, one study did note RT to be a statistically significant risk factor for subsequent IBD flare on multivariate analysis.

Conclusions: A review of reported acute and late toxicities suggests that patients with IBD should still be considered for definitive radiotherapy. Patient characteristics including IBD distribution relative to the irradiated field, inflammatory activity at the time of radiation, overall disease severity and disease phenotype in the case of CD (fistulising versus stricturing versus inflammatory only) should be considered on an individual basis when evaluating potential patients. When possible, advanced techniques with strict organ at risk dose constraints should be employed to limit toxicity in this patient population.

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Introduction

Inflammatory bowel disease (IBD) [i.e., Crohn's disease (CD) and ulcerative colitis (UC)] is a complex remitting and relapsing, immune-mediated disease of the gastrointestinal tract that affects approximately 1·5 million Americans, 2·2 million Europeans and a growing number of people in the Middle East and Asia where incidence is increasing.[1] Incidence rates for both CD and UC are believed to be rising with no singular identifiable cause since IBD develops at the crossroads of genetics, immunology, environment and the gut microbiome.[1]

In the fields of radiation oncology, urology and gastroenterology, there still exists a pervasive notion that the presence of IBD is a relative/absolute contraindication for radiation therapy (RT) to the abdomen or pelvis. Large-scale studies aimed at elucidating the toxicities of abdomino-pelvic irradiation in patients with IBD are essentially non-existent due to relative low incidence rates for IBD (North American incidence rates of 0–19·2 per million for UC and 0–20·2 per million for CD).[1] Most of the available literature consists of case reports or single-institutional retrospective studies with relatively small sample sizes. The purpose of this study is to compile and evaluate the currently available literature to better characterise the toxicities of RT in this small but important subset of patients.

Literature Review

A literature search was conducted using PubMed/MEDLINE with the following keywords for filtering of results: RT, brachytherapy, inflammatory bowel disease, Crohn's disease, ulcerative colitis and toxicity. The PubMed search yielded 1,206 results which were screened with the

Figure 1. Flow diagram for data collection following PRISMA convention
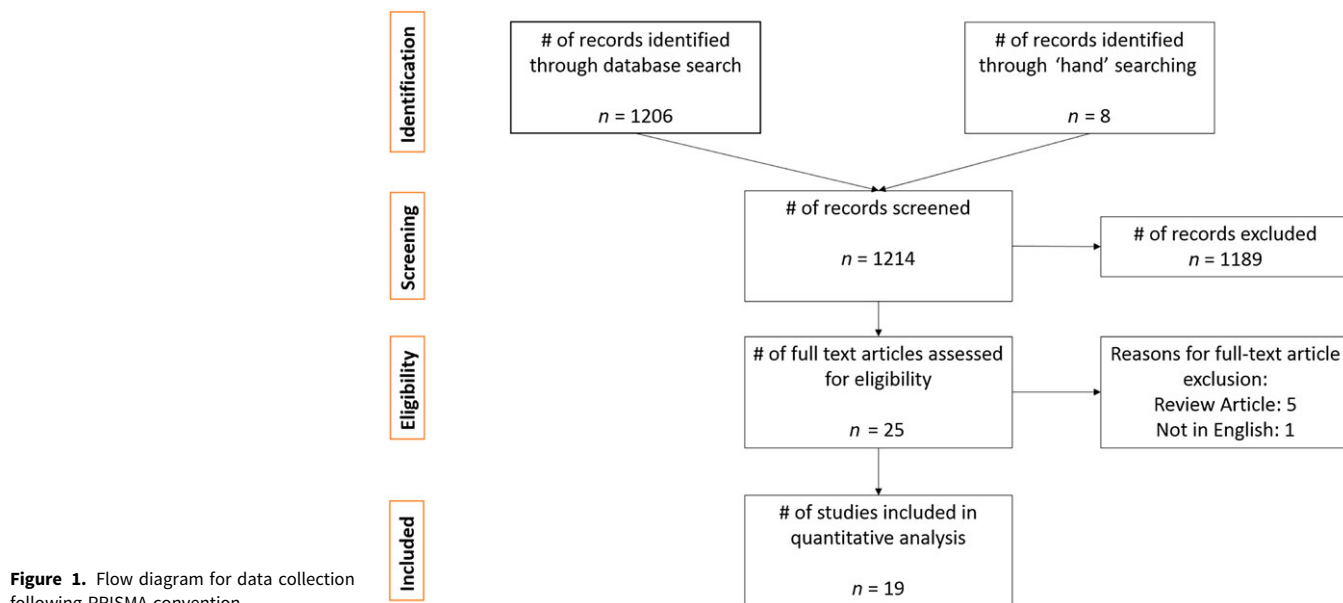
addition of 8 studies which were identified through hand searching. Case reports, and case series with a population less than 5 were excluded, and the number of full-text articles assessed for eligibility was 25. Among the full-text articles assessed for eligibility, 5 review articles and 1 non-English publication were excluded for a total of 19 studies meeting inclusion criteria to be selected for quantitative analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) conventions as shown in Figure 1. Three abstracts reported in the *International Journal of Radiation Oncology, Biology, Physics* (IJROBP) were included in the 19 studies reported in this review, those studies are denoted with an asterisk when appropriate in Tables 1–5.

Results

Overall, 19 studies were included in the review, and 17 of those studies are summarised in Table 3 with the remaining two studies summarised in Table 5. The total population of the studies summarised in Table 3 was 497 patients with 50·5% composed of UC and 37% composed of CD with an additional 12·5% carrying the diagnosis of IBD without a specific type indicated (Table 1). Roughly, 55% of the population was composed of patients with a gastrointestinal primary malignancy followed by prostate cancer which composed 40% of reported primary malignancies (Table 1). Of the studies that reported the modality of radiation, 70% of the population received external beam RT (EBRT) alone, 12% received brachytherapy alone, 3% received a combination of EBRT and brachytherapy and the remaining 15% was not specified (Table 2). Of the studies that reported treatment with EBRT alone, approximately 12% of patients were treated with intensity-modulated RT (IMRT), 18% with 3D-conformal techniques, 19% with IMRT or 3D-conformal radiotherapy (3D-CRT) without specification, 13% with 3 or 4 field technique, 4% with opposed anterior and posterior fields (AP/PA) and the remaining 34% without a specific technique documented (Table 2). Roughly, 49% of the population was taking some form of IBD medication at the time of therapy, and approximately 40% received concurrent chemotherapy (Table 1).

Tables 3A and 3B list individual study characteristics of the 17 included studies reported from 1999–2019. Of those 17 studies, 11 were retrospective studies without case–control and 6 studies compared those patients with IBD to matched or unmatched control patients. These case–control or matched studies are also summarised separately in Table 4. The mean radiation dose for each individual study is listed in Table 3A and varies based on site of primary malignancy. Acute and late radiation toxicities were reported using Radiation Therapy Oncology Group (RTOG) grading in 7 of 17 studies and Common Terminology Criteria for Adverse Events (CTCAE) grading in 7 of 17 studies with 3 of 17 studies using their own criteria. When including all primary malignancies, the reported range for acute toxicity ≥ grade 2 was 0–47% and acute toxicity ≥ grade 3 was 0–28% (Table 3B). When including all primary malignancies, the reported range for late toxicity ≥ grade 2 was 0–39% and late toxicity ≥ grade 3 was 0–29% (Table 3B).

Looking at trials specific to prostate cancer[2–8], the reported range for acute toxicity ≥ grade 2 was 25–33% for EBRT (2 studies reporting) and 0–38% for brachytherapy (4 studies reporting), and acute toxicity ≥ grade 3 was 0% (1 study reporting) for EBRT and 0–23% for brachytherapy (4 studies reporting) (Table 3B). Reported late toxicities in prostate cancer studies are also reported in Table 3B, with a range for late toxicity ≥ grade 2 of 6·3–17% for EBRT (2 studies reporting) and 0–38% for brachytherapy (4 studies reporting), and late toxicity ≥ grade 3 of 0% (1 study reporting) for EBRT and 0–15% for brachytherapy (3 studies reporting). When looking at those studies that only included gastrointestinal (GI) primary malignancies[9–12], namely rectal and anal cancers, the reported range for acute toxicity ≥ grade 3 was 0–28% and the late toxicity ≥ grade 3 was 13% (Table 3B).

Table 3A describes the individual study characteristics of the identified articles. Crohn's disease and ulcerative colitis are abbreviated as CD and UC, respectively. For brevity, common RT abbreviations were used: EBRT for external beam radiotherapy, IMRT for intensity modulated radiotherapy, 3D-CRT for 3D conformal radiotherapy, AP/PA for opposed anterior and posterior fields. In the case of brachytherapy, the commonly used abbreviations for low-dose rate (LDR) and for high-dose rate (HDR) have been

Table 1. Study Characteristics—Patient Factors

Type of IBD	N (Total = 497)	% of Total
Ulcerative Colitis	251	50·5%
Crohn's Disease	184	37%
Not Specified	62	12·5%
Concurrent Medications	**N**	**% of Total Reported**
IBD medications (steroids, 5-asa, immunomodulators)	176 of 363 reported	48·5%
Chemotherapy	106 of 266 reported	39·8%
Primary Malignancy	**N (Total = 473)***	**% of Total**
Anal, Rectal, Colon	259	54·8%
Prostate	187	39·5%
Other (Gynecologic, Genitourinary, Hepatobiliary)	27	5·7%

*Song et al. patients (N = 24) excluded from total because primary malignancy not specified.

Table 2. Study Characteristics—Radiation Therapy Modality and Techniques

Radiation Therapy Modality	N (Total = 497)	% of Total
EBRT	349	70·2%
Brachytherapy	61	12·3%
Brachytherapy + EBRT	13	2·6%
Not specified	74	14·9%
EBRT Technique	**N (Total = 283)**	**% of Total**
IMRT	42	12·03%
3D-CRT	63	18·1%
IMRT of 3D-CRT	66	18·9
3- or 4-field	45	12·9%
AP/PA	13	3·7%
Technique not specified	120	34·4%

employed. If a particular definition was used within the article of origin, that term was also used in the table for example, Willett et al.[13] specified 'conventional' as 1·8–2 Gy fraction size photon irradiation and 'specialised' as specific RT techniques (small fields, decubitus position, proton beam irradiation or scheduled rest periods during treatment) or surgical procedures (clips to delineate tumor bed, omentoplasty or Dexon mesh) to minimise or avoid small and large bowel irradiation. For the data reported from Bosch et al.,[12] short-course RT (SC-RT) is defined as pre-operative 5 Gy × 5 fractions given over a 5- to 7-day period, long-course RT (LC-RT) is defined as pre-operative radiation with 45–50 Gy given in 25–28 fractions of 1·8–2·0 Gy, and combined-modality chemo-radiation (chemo-RT) is defined as fluoropyrimidine-based chemotherapy concurrent with long-course radiation schedule. The number of patients receiving a defined RT modality was not listed in chart if not specified in source article. As mentioned earlier, the asterisk indicates data published in abstract form in

IJROBP. Table 3B displays the reported acute and late toxicities from the articles outlined in Table 3A. The following abbreviations were employed for statistically significant (SS), small bowel obstruction (SBO), side-effects (SE) and bowel movement (BM).

Several studies also compared toxicities with matched controls at their individual institutions[2,3,10–12,14] and are highlighted in Table 4. In an abstract published in IJROBP, Rhome et al. reported on 64 patients with IBD and a primary malignancy (mostly comprised of GI and prostate malignancies), with 42 of 64 patients treated with RT for their cancer and 22 of 64 treated without radiation.[14] There were no acute toxicities requiring hospitalisation and no significant differences in stricture formation, fistula formation, IBD flares or IBD medication escalation among the groups.[14]

Barnett et al. reported on prostate cancer patients with and without IBD treated with EBRT and found SS hazard ratios of 2·75 (1·38–5·48, $p = 0·004$) for loose stools and 3·59 (1·40–9·18, $p = 0·008$) for fecal urgency in those patients with IBD.[2] There was no statistical difference with regard to rectal bleeding, proctitis, sphincter control, stool frequency or urinary SE when comparing patients with IBD versus those without IBD.[2]

In another abstract published in IJROBP, Murphy et al. reported on 21 patients with IBD and prostate cancer treated with either brachytherapy or EBRT. When compared to those matched patients without IBD, there was no statistical difference in the acute or late toxicity ≥ grade 2.[3] They also reported that flare-free interval prior to RT, RT dose and modality (brachytherapy, 3D, IMRT) did not predict for GI toxicity or subsequent flare.[3] IBD medication use was the only predictor of acute > grade 2 GI toxicity at 57% for those requiring medication versus 7·7% for those not requiring medication ($p = 0·03$).[3]

Mudgway et al. reported on 71 patients with IBD and rectal cancer treated with EBRT compared with 71 matched controls with rectal cancer without IBD treated with EBRT, and 44 non-matched controls with IBD and rectal cancer treated without EBRT.[11] In the acute setting, there were no differences in breaks in RT, anti-diarrheal medication use or hospitalisations when compared to matched controls [although hospitalisations approached significance (adjusted OR 2·69, 95% CI, 0·88–8·22, $p = 0·08$)].[11] There was a SS higher rate of SBO (OR 15, 95% CI 1·9–115, $p = 0·009$) and higher rates of abdominopelvic adhesions that approached statistical significance (OR 3·6, 95% CI 0·98–13, $p = 0·05$) in the IBD + RT cohort.[11] When compared to the non-matched cohort with IBD treated without RT, there was no difference in long-term complications, suggesting that these adhesions or obstructions may be unrelated to RT.[11]

Chang et al. reported on 15 anal/rectal cancer patients with IBD treated with EBRT.[10] When compared with matched-control patients without IBD, there was no significant difference in rates of grade 2, 3 or 4 acute toxicity; however, when grouping acute and late toxicities grade 3 or greater, there was a SS higher rate versus the control group ($p = 0·02$).[10] Another study, by Bosch et al., looked at 161 patients with rectal cancer and IBD. Sixty-six of these patients were treated with some form of RT and the remaining patients served as matched control subjects.[12] Of the patients treated with RT, 32 received SC-RT (2500 cGy in 5 fractions over 5–7 days), 13 received LC-RT (4500–5000 cGy given in 25–28 fractions of 180–200 cGy), and 21 received LC-RT with concurrent chemotherapy.[12] In total, 0% of patients receiving SC-RT, 7·7% (n = 1) of patients receiving LC-RT, and 28·6% of patients receiving chemo-RT experienced acute grade 3 or greater toxicity ($p = 0·004$).

Table 3A. Individual Study Characteristics

Study	Year	N	IBD Type	IBD Meds	Primary Malignancy	RT Modalities/Techniques (N)	Mean Dose	Concurrent Chemo
Green et al.[9]	1999	15	Type not specified	Not Specified	15 Rectal	4-field (8) / 3-field (2) / AP/PA (5)	5040 cGy	13 out of 15
Willett et al.[13]	2000	28	CD 10 / UC 18	11 of 28	17 Colorectal / 7 Prostate / 4 Other	conventional (12) / specialised (16)	4010 cGy / 5110 cGy	11 out of 28
Song et al.[20]	2001	24	CD 15 / UC 7 / Type not specified 2	15 of 24	Primary not specified / 17 Abd/Pelvis / 8 Chest	EBRT	4500 cGy	15 out of 24
Barnett et al.[2]	2011	35	Type not specified	Not specified	35 Prostate	3- or 4-field to 6400 cGy / 4- to 6-field for additional 1000 cGy in 5 fractions if receiving boost	at least 6400 cGy	none
*Murphy et al.[3]	2015	21	CD 7 / UC 13 / Type not specified 1	7 of 21	21 Prostate	I-125 Brachytherapy: 4 / IMRT: 11 / 3D-CRT: 6	7600 cGy	none
*Glick et al.[17]	2014	61	CD 30 / UC 28 / Type not specified 3	31 of 61	18 Anal / 17 Rectal / 17 Prostate / 9 Other	conventional, 3D-CRT, and IMRT (numbers not specified)	Not specified—definitive and adjuvant doses	not specified
White et al.[21]	2015	19	CD 5 / UC 14	6 of 19	8 Prostate / 5 UGI / 3 Rectal/anal / 3 Liver	IMRT: 14 / 3D-CRT: 5	5400 cGy	8 of 18
Chang et al.[10]	2015	15	CD 4 / UC 8 / Type not specified 3	0 of 15	14 Colorectal / 1 Anal	IMRT, 3-4 field, AP/PA	4500–5400 cGy	13 of 15
*Rhome et al.[14]	2015	42	CD 22 / UC 20	Not specified	Prostate 35·9% / Rectal 18·8% / Anal 17·2% / Colon 14·1% / Other 14·2%	EBRT and Brachytherapy	5040 cGy	Not specified

(Continued)

Table 3A. (*Continued*)

Study	Year	N	IBD Type	IBD Meds	Primary Malignancy	RT Modalities/Techniques (N)	Mean Dose	Concurrent Chemo
Gestaut et al.[4]	2016	18	CD 2	14 of 18	18 Prostate	IMRT: 6	7020 cGy	None
							7020 cGy	
						3D-CRT: 6	I-125: 144 Gy	
			UC 16			LDR Brachytherapy: 6	Pd-103: 100-110 Gy	
Annede et al.[15]	2017	28	CD 13	21 of 28	12 Prostate	EBRT Alone: 18	5300 cGy	7 of 28
						3D-CRT: 17		
					8 Rectal	2D-RT: 8		
					5 Cervix	IMRT: 1		
					2 Anal	Brachytherapy: 2		
			UC 15		1 Endometrial	Brachytherapy + EBRT: 8		
Bosch et al.[12]	2017	66	CD 30	6 of 66	66 Rectal	3D-CRT or IMRT	2500 cGy	21 of 66
						Short Course (SC-RT): 32		
			UC 33			Long Course (LC-RT): 13	4500–5000 cGy	
			Type not specified 3			ChemoRT:21	4500–5000 cGy	
Mudgway et al.[11]	2019	71	CD 30	50 of 71	71 Rectal	IMRT: 10	5040 cGy	40%
						3D-CRT: 29		
			UC 41			Not noted on remaining: 32		
Grann et al.[5]	1998	6	CD 3	4 of 6	6 Prostate	I-125 Brachytherapy: 6	150 Gy	none
			UC 3					
Peters et al.[6]	2006	24	CD 7	11 of 24	24 Prostate	I-125 Brachytherapy: 15	I-125: 160 Gy	
						Pd-103 Brachytherapy: 6	Pd-103: 124 Gy	
			UC 17			Pd-103 Brachytherapy+EBRT: 3	Pd-103 + EBRT: 124 Gy + 45 Gy	
Pai et al.[7]	2013	13	CD 3	Not specified	13 Prostate	I-125 Brachytherapy: 13	144 Gy	none
			UC 10					
Mohammed et al.[8]	2018	11	CD 5	Not specified	11 Prostate	HDR Brachytherapy: 9	19-20 Gy single fraction	none
			UC 6			HDR Brachytherapy + IMRT: 2	15 Gy single fraction + 37·5 Gy IMRT	

Table 3B. Reported Acute and Late Toxicities

Study	Year	N	Toxicity Scoring	Acute Grade 2 or greater	Acute Grade 3 or greater	Late Grade 2 or greater	Late Grade 3 or greater
Green et al.[9]	1999	15	RTOG	not specified	20% (only 1 pt or 6·6% with GI toxicity)	not specified	13% (2pts both w/SBO)
Willett et al.[13]	2000	28	Acute: Cessation of RT due to SE's Late: Hospitalisation or surgery	Not specified	21%	not specified	29%
Song et al.[20]	2001	24	RTOG	Not specified	21%	not specified	8%
Barnett et al.[2]	2011	35	RTOG	Hazard Ratio 2·75(1·38–5·48, $p = 0.004$) for Loose Stools Hazard Ratio 3·59 (1·4–9·18, $p = 0.008$) for Fecal Urgency No SS hazard ratio for IBD in regards to rectal bleeding, proctitis, sphincter control, stool frequency or urinary SEs			
*Murphy et al.[3]	2015	21	CTCAEv3	25% (not SS from control)	Not specified	6·3% (not SS from control)	Not specified
*Glick et al.[17]	2014	61	RTOG	Not specified	11% - GI specific	Not specified	Not specified
White et al.[21]	2015	19	CTCAE	47% (37% - GI specific)	11% (5% - GI specific)	21% (5% - GI specific)	5%
Chang et al.[10]	2015	15	RTOG	Not specified	27%	Not specified	13%
*Rhome et al.[14]	2015	42	Not specified	Not specified	23·3% w/out increased BM frequency requiring medication	Not specified	Not specified
Gestaut et al.[4]	2016	18	CTCAE	33% (only 9 of 18 patients with toxicity data, looking at rates of diarrhea only)	0%	17% (looking at late proctitis only)	0%
Annede et al.[15]	2017	28	CTCAE	43% - GI-Specific	11% - GI-Specific	39% - GI-Specific	4% - GI-Specific
Bosch et al.[12]	2017	66	CTCAEv4	Not specified	0% (SC-RT) 7·7% (LC-RT) 28·6% (LC-RT + Chemo)	Not specified	Not specified
Mudgway et al.[11]	2019	71	Not specified	matched case–control of VA population: N = 156 (71 w/out IBD + RT versus 71 w/out IBD + RT versus 44 w/out IBD w/out RT) No statistical difference in required treatment breaks or need for anti-diarrheal during treatment compared to control arm without IBD, higher rate of SBOs and a trend toward higher rate of adhesions			
Grann et al.[5]	1998	6	RTOG	0%	0%	0%	0%
Peters et al.[6]	2006	24	CTCAE	4%	0%	17%	0%
Pai et al.[7]	2013	13	RTOG	38%	23%	38%	15%
Mohammed et al.[8]	2018	11	CTCAEv4	0% - GI-Specific	0% - GI-Specific	Not specified	Not specified

Table 4. Summary of Results for those studies with matched controls

Study	Acute Toxicity	Late Toxicity	Notes
*Rhome et al.[14]	No acute toxicities requiring hospitalization	Stricture: 4·8 versus 0% (NS) Fistula: 2·4 versus 9% (NS) IBD Flare: 2·4 versus 4·5% (NS) IBD Medication Escalation: 0·0 versus 4·5% (NS)	
Barnett et al.[2]	Not specified	Loose Stools: HR 2·75 (1·38–5·48, $p = 0.004$) Fecal Urgency: HR 3·59 (1·40–9·18, $p = 0.008$)	
*Murphy et al.[3]	≥**G2** 25 versus 8·3% $p = 0.11$ IBD medication use was the only predictor of acute > G2 GI toxicity at 57 versus 7·7% ($p = 0.03$)	≥**G2** 6·3 versus 10·2% $p = 0.83$	Flare free interval prior to RT, RT dose and modality (brachy, 3D, IMRT) did not predict for GI toxicity or subsequent flare
Mudgway et al.[11]	No differences in: RT breaks anti-diarrheal medications or hospitalisations (although increased hospitalisations approached significance for the IBD-RT group, $p = 0.08$)	Small bowel obstruction: OR 15 (1·9–115, $p = 0.009$) Abdominopelvic Adhesions: OR 3·6 (0·98–13, $p = 0.05$) *no difference in late complications when compared to the IBD group that received no RT	No differences found in other acute or late toxicities (e.g., fistulas, strictures, proctitis, perforation)
Chang et al.[10] (Lower GI toxicities)	**G2:** 73 versus 50% $p = 0.13$ **G3:** 20 versus 7% $p = 0.19$ **G4:** 7 versus 0% $p = 0.13$	**G2:** Not specified **G3:** Not specified **G4:** 13 versus 0%	≥**G3** (Acute or Late) higher in IBD versus control $p = 0.02$
Bosch et al.[12]	≥**G3** **SC-RT:** 0% (0/32) **LC-RT:** 7·7% (1/13) **Chemo-RT:** 28·6 % (6/21) $p = 0.004$		

Table 5. Multivariate logistic regression model of IBD flare predictors in 1 year following prostate cancer treatment (taken from Refs.[16,18])

From Kirk et al.[19]			
Covariate	Adjusted OR	95% CI	P value
Flare in year preceding therapy for prostate cancer	12·5	5·4–29·2	<0·001
D'amico risk group	0·9	0·5–1·5	0·71
Radiation Therapy	1·5	0·6–3·6	0·37
From Feagins et al.[18]			
Covariate	Adjusted OR	95% CI	P value
D'Amico Risk Group	0·38	0·15–0·98	0·046
Radiation Therapy	4·83	1·15–20·26	0·031
Charlson Comorbidity Index	1·03	0·75–1·42	1·42

IBD activity after therapy

There is scarce information regarding the effect of RT on IBD activity following completion of treatment. Willett et al. found no SS difference in toxicity frequency related to IBD activity.[13] There were two studies that reported on IBD flares in the year following RT.[15,16] Glick et al. reported in abstract that IBD type, active use of IBD medications and previous IBD-related surgery were not predictive for acute toxicity on univariate analysis.[17] As mentioned previously and outlined in Table 4, Murphy et al. found IBD medication use to be a predictor for acute > grade 2 toxicity (57·1% versus 7·7% $p = 0·03$) but found the flare-free interval prior to RT to not be predictive for subsequent flare.[3]

There were two larger studies that reported on IBD flares in the year following RT.[16,18] Kirk et al. analysed a population of 240 men with prostate cancer and a diagnosis of IBD at the time of cancer diagnosis treated in the United States Department of Veterans Affairs (VA) system.[16] In the VA population, it was found that patients with IBD and prostate cancer were much more likely to receive surgery than RT compared to those patients without a diagnosis of IBD treated in the same system, 41 versus 28% ($p < 0·001$).[16] Among the patients with IBD and prostate cancer, there was no SS difference in flares occurring in the year following treatment between the surgery alone, RT alone and active surveillance/androgen deprivation therapy cohorts, with a flare rate of roughly 18%.[16] The only predictor for flare following therapy was the presence of a flare in the year preceding treatment (OR 12·5, 95% CI 5·4–29·2), $p < 0·001$.[16] There was no increased risk of flare on multivariate analysis based on D'Amico risk group or RT status (Table 5).[16]

Another group also looked at a similar population within four VA hospitals in Texas and Virginia.[18] In this study, 100 patients with IBD (29% CD, 66% UC and remainder with undefined colitis) with prostate cancer were identified. In total, 47% of patients underwent RT (of these 72% EBRT and 28% brachytherapy). Of the 53 patients who did not undergo RT, 77% underwent surgery with the remainder receiving androgen deprivation therapy or chemotherapy.[18] There was no statistical difference in age, race, IBD type or cancer stage between the RT group and those treated with other modalities. On univariate analysis, there was no statistical significance in IBD flares, IBD hospitalisations or IBD-related surgeries following therapy, as well as no differences seen in overall survival.[18] However, on multivariate analysis (as shown in Table 5), RT was identified as a risk factor for subsequent IBD flare. Interestingly, D'Amico risk group was also associated with flare on multivariate analysis.

Annede et al. reported on 28 patients with various malignancies treated in France.[15] In this study, the severity of IBD was assessed with the Harvey Bradshaw Index (HBI) and the Mayo Index for CD and UC, respectively, with severe IBD being classified as HBI > 16 or Mayo > 7, moderate IBD as HBI 8–15 or Mayo 5–6, mild IBD as HBI 5–7 or Mayo 2–4 and remission if less than the aforementioned thresholds. During follow-up after completion of RT, the median scores for patients within 6 months of treatment was Mayo of 4 and HBI of 2 for UC and CD, respectively, and after 6 months those scores improved to 3 and 1 respectively. Within the first 6 months following treatment, 50% of patients were classified as 'in remission', and this improved by 61% after 6 months. Only two patients experienced severe IBD symptoms in follow-up, both of which were patients with prostate cancer (one treated with EBRT to a dose of 7400 cGy, and one treated with EBRT, 4600 cGy to prostate and seminal vesicles with 1400 cGy HDR brachytherapy boost).

Discussion

Historically, IBD has been considered a contraindication for RT largely related to concerns of increased acute and late toxicities. Further compounding the issue is the fact that most of the existing studies have small patient populations, employ different toxicity-reporting conventions, involve numerous disease sites and were largely performed in an era of RT predating the widespread adoption of advanced techniques such as IMRT. Elucidating the improvement of SE profile with the widespread adoption of advanced radiation techniques (such as IMRT) is difficult with the current literature available since most series describe patients treated over a wide range of time.

White et al. reported lower acute ≥ grade 2 toxicity in the IMRT treated patients compared to those treated w/out 3D-CRT (14 versus 100% $p = 0·002$).[21] Feagins et al. attempted to demonstrate this effect.[18] In their study, when analysing 100 VA patients with IBD and prostate cancer from 1996 to 2015, there was no statistical difference in the rate of subsequent IBD flares in those treated in the 1st decade (1996–2005) versus the 2nd decade (2006–15), nor was there a difference in flares between those getting treated with and without radiation in the 1st versus 2nd decade.[18] Although this study does not show a difference when looking specifically at IBD flares, it is assumed that other GI/GU grade 3 toxicities would have improved over that time period due to the adoption of more advance delivery modalities.

Only one meta-analysis has been performed regarding this topic and was published in 2019 by Lin et al.[19] Using data from 8 of the 17 studies included in this report,[6,7,9,10,12,13,20,21] the rate of acute toxicity grade 3–5 was calculated to be 14% (7–22·4) and late toxicity grade 3–5 was calculated at 10·2% (3·2–19·7).[19] These figures are within the range of the values reported in Table 3B (up to 27% for acute ≥ grade 3 toxicities and up to 29% for late ≥ grade 3 toxicities).

It is instructive to compare the above rates of toxicity to those seen in modern studies of patients without IBD treated with RT. RTOG 04-15 randomised patients with prostate cancer to receive either conventionally fractionated EBRT versus hypofractionated EBRT, reporting rates of acute ≥ grade 3 GI and GU toxicities of 0·6 and 2·4% for the hypofractionated arm and 0·8 and 3·3% for the conventional arm. Rates of late ≥ grade 3 GI and GU toxicities were 2·6% and 2·3% for hypofractionated RT and 4·1% and 3·5% for conventional RT for patient treated with IMRT or 3D-CRT.[22]

The RTOG 98-11 trial which randomised patient with anal cancer to RT plus 5-FU and mitomycin or RT plus 5-FU and cisplatin reported rates of acute ≥ grade 3 GI toxicity of 36·6% and 46·6% between trial arms, respectively. Late ≥ grade 3 GI toxicity for RTOG 98-11 occurred in 3% and 2·5% of patients repectively.[23] The RTOG 05-29 trial which utilised dose-painted IMRT to treat anal cancer with 5FU and mitomycin reported grade ≥ 3 GI toxicity in 11 of 52 (21·1%) patients—decreased compared to RTOG 98-11.[24]

Late effects, strictures and fistulas

One of the primary concerns for patients with IBD receiving RT is the development of late toxicities such as fistulas or strictures. These are difficult toxicities to approximate since either can be the result of the radiation or the IBD itself. Mudgway et al. found no difference in stricture or fistula formation when compared to matched controls receiving RT or unmatched patients with IBD receiving no RT.[11] Rhome et al. reported similar results, finding that there was no SS difference in the formation of fistula or stricture, IBD flares or IBD medication escalation between groups of patients with IBD receiving radiation and matched controls with IBD treated without RT.[14]

IBD activity

Although there is limited supporting evidence, there seems to be little effect of RT on the severity or activity of IBD. One study,[16] found that the activity of disease in the year preceding therapy was the best predictor of disease activity after therapy; however, another study[3] reported that the flare-free interval prior to RT was not predictive of GI toxicity or subsequent IBD flare. Yet, another study[15] found that most patients remained in remission in the year following RT, improving from 50% at 6 months to 60% at a year, with only two patients experiencing severe IBD symptoms following radiation. Feagins et al. did find RT to be a SS risk factor for subsequent IBD flare on multivariate analysis.[18] Understanding how active or well-controlled a patient's IBD is prior to therapy is likely the best way to estimate risk of flare following RT. When available the number of patients on IBD medications at the time of treatment was listed for each study in Table 3A. However, information on which IBD medications were being used was limited and most studies either grouped all IBD medications together or did not compare outcomes based on specific IBD medication use. In clinical practice, however, the class of medication used can indicate how severe or active the IBD actually is (e.g., use of biologic as a surrogate for severe disease). There was a

significant number, roughly 50%, of patients across all studies examined who were not taking IBD medications, but it is unknown if these patients were in remission or if maintenance therapies were stopped specifically for cancer therapy as is sometimes done, especially in the case when concurrent chemotherapy is used.

Concurrent chemotherapy

It is well established that the addition of chemotherapy to radiation or vice-versa will result in increased toxicity; however, it is not known to what extent this effect will manifest in IBD patients. In some cases, systemic therapy with its immunomodulation can improve IBD symptoms even while increasing toxicity in other areas. Further complicating this point within the literature are the rather small sample sizes and differing disease sites. For example, it is exceedingly rare for a prostate cancer patient, unless metastatic, to receive chemotherapy, whereas most protocols for GI malignancies include chemotherapy, see Table 3A. In the only study to report the toxicity outcomes for those receiving RT or RT plus chemotherapy, the addition of chemotherapy to LC-RT increased acute ≥ grade toxicity by roughly 20%.[12] This increase in toxicity was not different from the toxicity seen in the matched control group.

Proton therapy

Unsurprisingly, there is a lack of information regarding proton therapy in this patient population. Willett et al. reported on 28 patients with IBD who received RT.[13] Of these patients, 12 were treated with conventional radiation and 16 were treated with a combination of specialised techniques (e.g., proton therapy, small fields, decubitus position or scheduled breaks).[13] There was a SS difference in severe late effects between patients receiving conventional treatment and those receiving specialised radiation techniques (50 versus 13%, $p = 0·02$).[13]

Conclusions

Although limited, current literature demonstrates that definitive radiation can be delivered effectively and safely to patients with IBD with acceptable toxicity profiles. Though not consistently reported, patient characteristics including IBD distribution relative the irradiated field (e.g., isolated small bowel disease versus colon and rectum involvement), inflammatory activity at time of radiation, overall disease severity and finally disease phenotype in case of CD (fistulising versus stricturing versus inflammatory only) are likely to impact the incidence of acute and late radiation toxicity, and should be taken into account on each individual basis when evaluating potential patients. When possible, advanced techniques with strict organ-at-risk tolerances should be employed to limit toxicity in this patient population.

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