



Inflammatory bowel disease-associated malignancies and considerations for radiation impacting bowel: a scoping review

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Background: Inflammatory bowel disease (IBD), subdivided into Crohn's disease (CD) and ulcerative colitis (UC), is an auto-inflammatory gastrointestinal condition with an established increased risk of certain malignancies. Compared to sporadic cancers in the general population, IBD-associated malignancies present unique challenges to providing quality care. Radiation therapy (RT) targeting IBD-associated malignancies may directly impact inflamed bowel, with special considerations for the risk of toxicities. Historically, patients with IBD have been less likely to receive radiotherapy in proximity to bowel due to a poor understanding of the potential for acute and chronic toxicities and unclear treatment outcomes. We present a scoping review, to more fully assess IBD-associated malignancies and their treatment. As opposed to a systematic review, this approach allows us to analyze the broadest range of literature, including experimental and non-experimental research, and reflect on current guidelines and practices.

Methods: Literature search: a systematic, scoping search of published literature was conducted using applicable PRISMA scoping review (ScR) guidelines. The literature search was conducted on PubMed and was searched systematically by screening all publications from January 1990 to June 2021. Citations from the included articles were also manually searched. Relevant National Comprehensive Cancer Network guidelines were reviewed. Final query was December 2021 in editing. Articles were selected for full text reading if the abstract reported on malignancy in IBD or bowel toxicities.

Results: The pelvic malignancies found in the IBD patient population, including colorectal carcinoma, anal carcinoma, lymphoma, small bowel adenocarcinoma (SBA), and prostate cancer (PCa) are outlined in this scoping review. Additional cancers that have a contested relationship with IBD, including cervical, bladder, and upper GI cancers, are also explored. This review provides literature guided recommendations on the eligibility of patients with IBD to receive RT, management of IBD during and after treatment, and counseling for radiation-induced toxicities.

Conclusions: After review of the literature, IBD should not be considered an absolute contraindication to radiation therapy, given the lack of evidence for increased toxicities, and the evolution of RT techniques which limit radiation dose to the bowel.

Keywords: Inflammatory bowel disease (IBD); radiation; bowel toxicity; inflammation; Scoping Review

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Introduction

Inflammatory bowel disease (IBD) is a complex auto-inflammatory condition of the gastrointestinal tract subdivided into Crohn's disease (CD) and ulcerative colitis (UC). Symptoms include diarrhea, constipation, hematochezia, nausea, vomiting, and weight loss; ultimately resulting in inflamed segments of bowel, ulceration, fistulation, and fibrosis/stricture. IBD is marked by fluctuating episodes of flare and remission, usually reflecting elevations and declines in systemic and local inflammatory markers. It is speculated that this prolonged state of inflammation may result in an increased rate of malignancy seen in patients with IBD (1).

Compared to sporadic cancers in the general population, IBD-associated malignancies present unique challenges to providing quality care. The presence of preexisting diseased and inflamed tissue elicits concerns when selecting therapeutic options. For the Radiation Oncology team, it is critical to understand the risk and presentation of IBD-associated malignancy, the potential for flares in the peri-radiation period, the heightened concern for treatment toxicities, and the expected oncologic outcomes related to IBD-associated malignancy.

Historically, patients with IBD are less likely to receive radiation therapy (RT) due to concerns for increased rates of toxicities and flares (1-6). National Comprehensive Cancer Network (NCCN) guidelines rate active inflammatory disease of the rectum as an absolute contraindication to external beam radiation therapy (EBRT) for prostate cancer (PCa) and inactive UC as a relative contraindication (4). Many have extended this guideline to additional sites and modalities in practice, thus avoiding use of RT in patients with IBD. However, updated analysis has suggested that IBD should not be considered a contraindication for radiation, even in systems neighboring potentially impacted bowel (7-13). Modern improvements in RT conformality, along with documented similar acute and late toxicity rates compared to patients without IBD, suggest that RT could be considered as a treatment option in IBD-associated malignancies (8,9,14-16). Cumulative rates of acute grade ≥ 3 toxicities across all cancers in patients with IBD are 14-27%, similar to the general population rates (9,14,17-19). The cumulative rates of late grade ≥ 3 toxicities across all cancers in patients with IBD are 0-29%, also comparable to rates in the general population (9,14,17-19). Case reports of patients with IBD treated with pelvic RT are abundant, highly suggesting that despite guidelines and historical

opinion, patients with IBD may, in fact, receive RT as part of their care and determined by their care teams.

This scoping review is organized to describe six categories of malignancy (colorectal carcinoma, anal carcinoma, lymphoma, small bowel adenocarcinoma, prostate cancer, and cancers with no proven association) that have a proposed relationship with IBD (*Figure 1*) and in which treatment must take into consideration the proximity to nearby bowel impacted by IBD, with a special emphasis on any modifications to the standard treatment planning. It is followed by a review of IBD management considerations during RT and a discussion of the findings. This review assesses the available experimental and non-experimental literature available on the topic, including practice recommendations and available guidelines. We present the following article in accordance with the PRISMA-ScR reporting checklist (20) (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-138/rc>).

Methods

A systematic, scoping search of published literature was conducted using applicable PRISMA ScR guidelines (20). The literature search was conducted on PubMed and was searched systematically by screening all publications from January 1990 to June 2021. Citations from the included articles were also manually searched. Relevant National Comprehensive Cancer Network guidelines were reviewed. Information regarding keywords is summarized in *Figure 2*. Final query was December 2021 in editing. Articles were selected for full text reading if the abstract reported on malignancy in IBD or bowel toxicities. Full English text of the relevant studies was retrieved for further selection.

Inclusion/exclusion criteria

Relevant clinical studies, meta-analyses, case reports, and reviews were included. Reviews were included to better reflect the reasoning and recommendations in the literature that guide decision making in providing RT for patients with IBD. Articles including only familial malignancies, or malignancies with no concern for bowel toxicities during treatment were excluded. The inclusion of case reports and studies with low power reflects the limited availability of data and may introduce a potential for bias in the published literature.

An example of a search conducted as part of this review is as follows: PubMed, date range January 1990 to June 2021, language English, search term "IBD Anal Cancer",

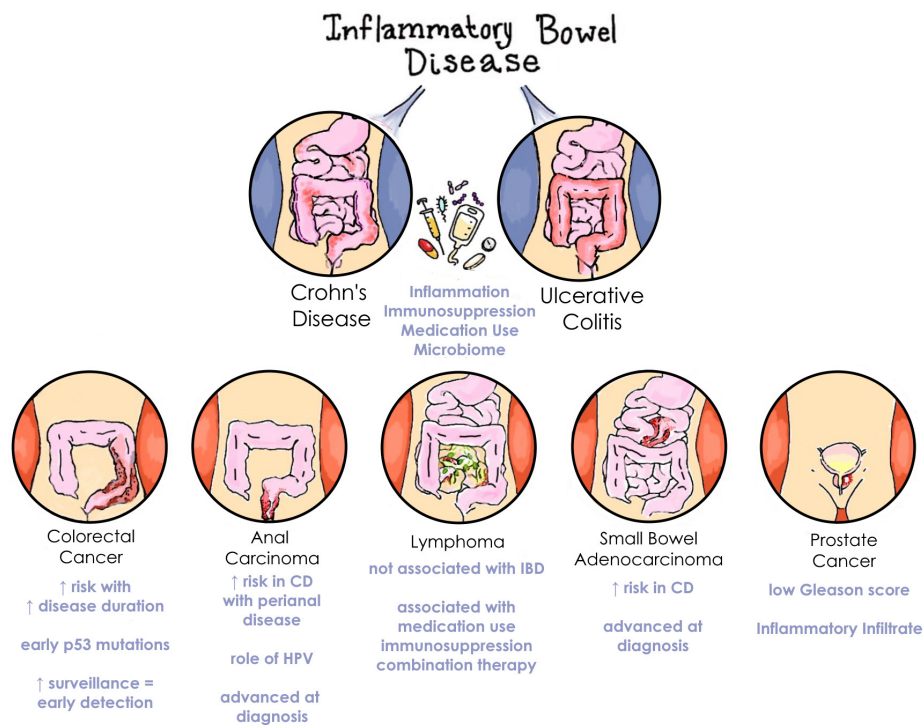


Figure 1 Cancers associated with inflammatory bowel disease. Illustration of the subtypes of inflammatory bowel disease, Crohn's disease and ulcerative colitis, and their prototypical anatomical inflammatory distribution. CD can occur throughout the digestive tract in a patchy distribution. Ulcerative colitis is limited to the large intestine. Both diseases share risk factors which are potential contributors in the development of the cancers shown. These cancers have special considerations during treatment due to their proximity to bowel impacted by IBD. IBD, inflammatory bowel disease; CD, Crohn's disease; HPV, human papilloma virus.

yields 88 titles. After scanning titles for relevance, 21 abstracts were read. Seven articles were excluded based on discussion of IBD-associated anal cancers, not only IBD or sporadic anal cancers. Fourteen full text articles were read in full, and 7 citations were found that specifically addressed IBD-associated anal cancers pathogenesis, prognosis, and treatment, and were ultimately included in this review.

IBD-associated malignancies with proximity to bowel

Colorectal carcinoma (CRC)

CRC is a well-established malignancy associated with IBD, but is not frequently treated with RT. Neoplastic and CRC risk is increased with a diagnosis of colitis involving at least 1/3 of the colon and a duration of disease greater than 7–10 years (21,22). The risk is greater in individuals diagnosed with IBD at a young age (23,24), those with primary sclerosing cholangitis (PSC) (25), and those with fistulizing

CD (21,26–28). CRC presents at a mean age 7.7 years younger in patients with IBD than in sporadic cases (29), but with a similar 5-year survival rate (30–32). Historically, patients with IBD present with high grade tumors and 20–24% are mucinous tumors; however, updated studies have shown a 50–60% prevalence of low-grade CRC at diagnosis (32,33).

IBD-associated CRC exhibits unique patterns of development and progression. Whereas sporadic CRC typically develops from a dysplastic precursor adenoma, IBD-associated CRC develops from precursors that can be polypoid, flat, localized, or multifocal (34). The lesions tend to develop in areas of histologic or gross inflammation (35). Reepithelization of ulcerated or damaged tissue with genomically unstable clones can create large or multifocal fields of high neoplastic potential. IBD-associated CRC has a distinct pattern of molecular and genetic changes, acquiring early p53 mutations (36,37) and having hypermethylation of CpG islands preceding dysplasia (38).

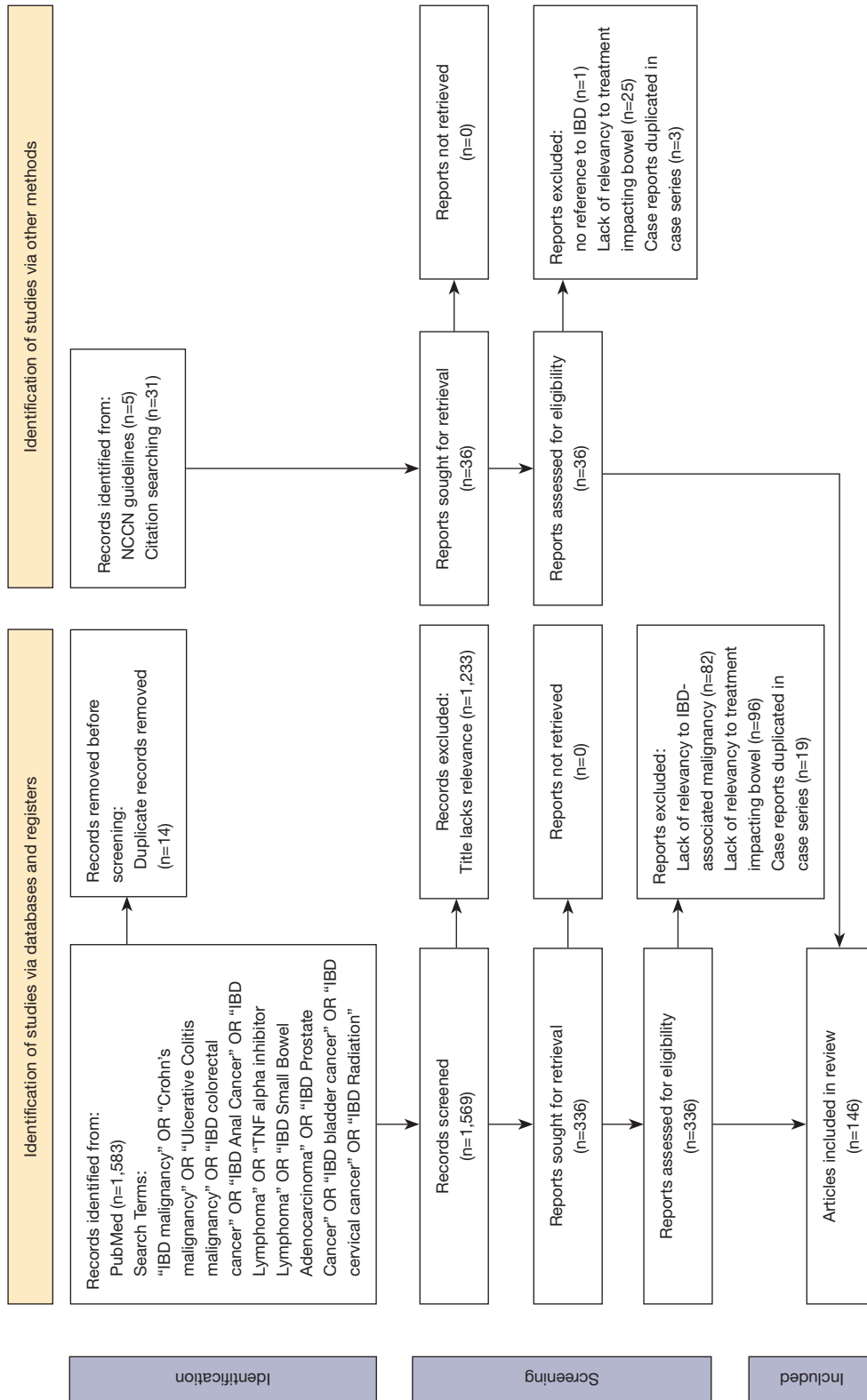


Figure 2 Literature search flow diagram. A modified PRISMA diagram showing keywords used in the literature search of this review. IBD, inflammatory bowel disease

Based on this aggressive progression, surveillance guidelines have been developed specifically for the IBD population, including yearly colonoscopy in high-risk patients (39). It is important for oncology providers to be aware of these heightened guidelines for their patients with IBD, and to coordinate with their gastroenterologist during follow-up.

Surgical management remains the mainstay of treatment for IBD-associated colon cancer, with adjuvant chemotherapy based on staging, with little established role for RT. In sporadic colon cancer, RT is typically reserved for locally advanced and recurrent disease. Given the high rate of synchronous tumors and poor differentiation, a total proctocolectomy (TPC) with ileal-pouch anal anastomosis (IPAA) is recommended for patients with IBD, in contrast to a segmental approach often utilized in sporadic cases (29). However, TPC with IPAA has significant implications for mortality and quality of life. IBD adversely affects surgical outcomes, with higher rates of complications like wound infections, deep vein thrombosis, postoperative hemorrhage, and poor wound healing (40). Moreover, the surgical removal of the colon does not cure CD, and patients may continue to experience inflammatory symptoms in the small bowel and suffer heightened nutritional and electrolyte disturbances postoperatively.

Sporadic rectal cancers, in contrast to non-rectal colon cancers, are frequently treated with preoperative RT and concurrent chemotherapy; however, IBD-associated adenocarcinomas occur less frequently in the rectum (OR 0.827) (41). In cases where RT is utilized for IBD-associated rectal cancer, dosing is limited by small bowel tolerance. A total of 0%, 7.7%, and 28.6% of patients experienced acute grade ≥ 3 toxicity for short-course radiation therapy, long-course radiation therapy, and chemoradiotherapy respectively (42). This measure of toxicity was assessed retrospectively in 66 patients in the Dutch pathology registry, and while significant, likely warrants further investigation in a larger population. While hospitalization rates for patients with IBD and rectal cancer during RT compares to those with sporadic rectal cancer, their need for RT breaks and anti-diarrhea medicines is not significantly higher (43), suggesting the concern and close monitoring of IBD patients may lower the threshold to recommend hospitalization. There is some suggestion that malignancies in the rectum are associated with higher rates of IBD flare in the peri-radiation period compared to other sites in the bowel (44). When treating the colon, it may be helpful to treat the patient in the prone position to better spare uninvolved bowel. For rectal cancers, a meta-analysis of eight articles and 127 patients supports that utilizing proton

beam therapy compared to photon-beam RT significantly reduced the dose to nearby small bowel (45).

Anal carcinoma

Anal carcinomas are uncommon in the general population and are modestly increased in the IBD population (2). It is more common in women with IBD, with a median age of onset younger than the general population at 42 years (2). In patients with CD, 85% have a history of peri-anal disease and 80% of patients present 10 years or more from IBD diagnosis. Anal carcinomas can be difficult to diagnose in CD, complicated by underlying sepsis, fistulae or fissures, and may present at more advanced stages than the general population (46,47).

The pathogenesis of IBD-associated anal cancers may be multifactorial, including chronic inflammation, human papilloma virus (HPV) infection, decreased defensin production, and drug-induced immunosuppression from IBD therapies as shown in *Figure 3* (48). While higher rates of HPV infection are seen in squamous cell carcinoma (SCC) patients with IBD, the relationship is not well understood (49). CD patients are more likely to have abnormal anal cytology regardless of HPV status (49). Defensins, which have been shown to suppress HPV, are lower in CD, leading some to suggest this as a possible explanation for elevated rates of anal SCC (48). The general population has additional risk factors for the development of anal carcinoma, including a history of human immunodeficiency virus (HIV), sexually transmitted infections (STIs), and smoking.

Further complicating the clinical picture, anal cancers in IBD can arise from the native anal tissue, or from fistulas, strictures, and other diseased lesions. Active perianal disease involvement, particularly the presence of fistulas, predominates the documented cases of IBD-associated anal SCC (50). It is theorized that the fistulous tract creates an ideal environment for HPV driven dysplasia (2,46). Adenocarcinomas of fistula tracts arise from migrated columnar rectal tissue, and therefore are more histologically similar to rectal tissue than to glandular tissue (51).

This complex clinical picture is compounded by poor outcomes for IBD-associated anal carcinomas. While sporadic anal carcinomas are usually treated with chemoradiation, 73% of the 33 IBD-anal SCC patients in a systematic review received radical surgery as first line treatment (2). Given the overall low occurrence rate of anal SCC, it is not surprising that even systematic reviews have a small population, however, this creates limitations in

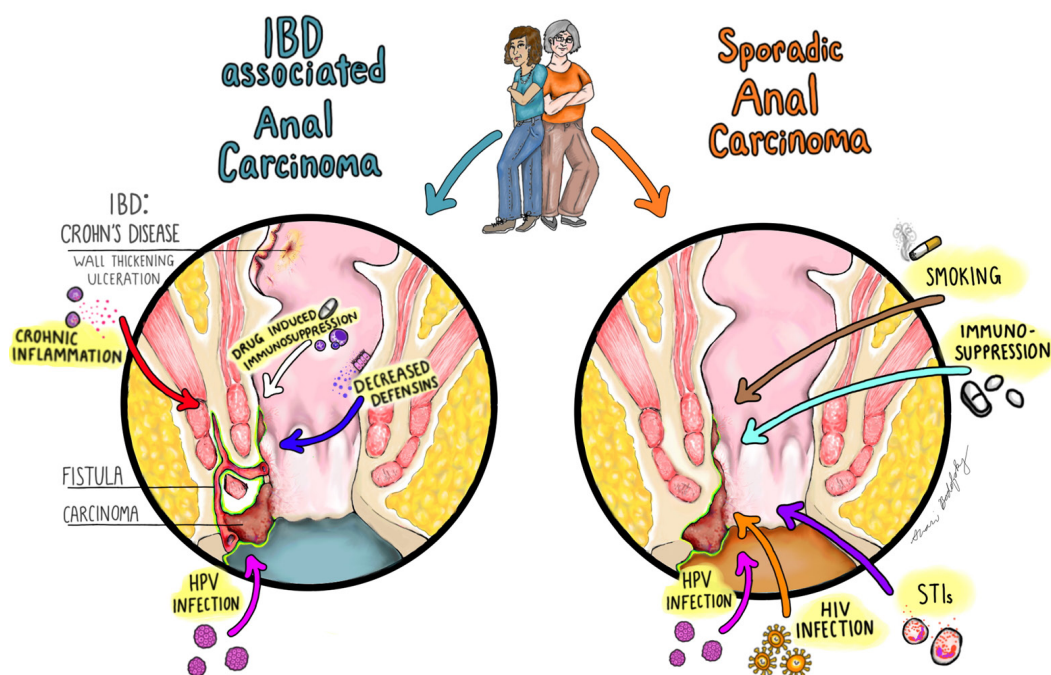


Figure 3 IBD-associated versus sporadic anal carcinoma. IBD-associated anal carcinoma has some notable differences in pathogenesis compared to sporadic anal carcinoma in the general population. While both groups share the major risk factor of HPV infection, it is noted that in patients with IBD, the presence of fistulas, perianal disease, and lower presence of defensins may put the patient at higher risk for failure to clear the infection. Immunosuppression, such as in transplant recipients or in patients with IBD utilizing immunosuppressive drugs as therapy, is also associated with increased anal carcinoma. For the Crohn's disease patient, chronic inflammation may contribute to neoplasia. Ultimately, IBD-associated anal carcinoma develops at a younger age compared to the general population. The inflammation of receptive anal intercourse, ongoing STIs like gonorrhea and chlamydia, and smoking are associated with increased rates of anal carcinoma in the general population. IBD, inflammatory bowel disease; HPV, human papilloma virus; HIV, human immunodeficiency virus; STIs, sexually transmitted infections.

the power of the data which could be useful in uncovering subtle differences in outcome. Overall survival at 5 years is just 37% in IBD-associated cases and median disease-free survival is 4 years (2). The current literature has ambiguous suggestions as to why IBD patients undergo surgical management at such a high rate- citing potential increased morbidity of radiotherapy in IBD patients, inability to follow response, potential reduced anal function, and preceding sepsis (46). However, these concerns are not backed by data, and appear to be mostly speculative. Although the data is limited, it is suggested that there were improved outcomes in IBD patients who received multimodal treatment-frequently abdominoperineal resection (APR) with chemoradiation (46). Therefore, despite a history of avoiding RT in these patients, we recommend a multimodal approach to treating IBD-associated anal carcinoma, including the utilization of RT.

The advantage of utilizing RT includes treating lymph nodes that may not be dissected with APR and starting with chemoradiation may reduce the need for surgery or allow for more conservative techniques.

Lymphoma

While lymphomas do not exclusively occur in proximity to bowel, the presence of lymphoma in structures adjacent to the bowel elicits concerns for RT planning in patients with IBD. Our choice to include lymphomas in this review also reflects the historic belief that IBD may increase the risk of lymphoma, as in rheumatoid arthritis (RA) and lupus. However, large population-based studies did not reveal a significant relationship between IBD and lymphoma (52-55). Nonetheless, many of the medications used in IBD management have an association with lymphoma

development, resulting in a higher incidence of lymphoma in the IBD population.

Medications used for IBD therapy with suspected increased lymphoma risk include corticosteroids (56-60), methotrexate (54), thiopurine analogues (61-63), and some tumor necrosis factor (TNF)-alpha inhibitors [infliximab (60,64), adalimumab (60,65)]. Certolizumab pegol has not been linked with an increased risk of lymphoma (60,66). Notably, there is a particular concern for an increased risk of aggressive and often fatal hepatosplenic T-cell lymphoma (HSTCL) with combination biologic and immunomodulator therapy, however its occurrence has been documented with azathioprine monotherapy as well (52,67,68). It is particularly associated with anti-TNF therapy in combination with immunomodulators (67).

Immunosuppressive therapies and biologics have increased lymphoma risk for the IBD patient and may necessitate therapy changes in the face of a new diagnosis of malignancy. Stopping immunosuppressive therapies during treatment may be advisable to minimize cancer progression but may present a significant opportunity for IBD flare activity. As this could ultimately necessitate breaks and delays in RT and chemotherapy, the decision to halt immunosuppressive therapy must be made with caution, and alternate therapies should be considered in their absence. Discussion among oncology and gastroenterology providers is pivotal to managing patients optimally.

As radiation doses for lymphomas have decreased, it is generally safer with fewer toxicities, and should not require significant alterations in planning for patients with IBD.

Small bowel adenocarcinoma (SBA)

SBA is a rare cancer with greatly increased risk in CD patients, usually presenting in advanced stages (69-74). This same correlation has not been established for patients with UC (75,76). As patients with CD can experience extended periods of inflammation in the small bowel, a possible mechanism of pathogenesis has been proposed as inflammation leading to dysplasia and subsequent adenocarcinoma (48,77,78). Studies have revealed the presence of K-RAS, APC, and MMR genetic mutations in SBA, paralleling CRC (48,79-81). Markers that have been specifically indicated in CD patients with SBA include P53, K-Ras, and signs of microsatellite instability (48,78,82). There is considerable disagreement on the prognosis of CD-associated SBA, largely owing to poor follow up and a lack of matched controls (48,83-86).

For this rare but threatening cancer, standard of treatment includes laparoscopic removal of identified malignancies (48,87). Adjuvant chemotherapy to prevent disease recurrence is usually employed in the setting of lymph node involvement; however, studies have not shown an improvement in disease free or overall survival (48,88). Given the uncommon nature of SBA, and the infrequency of RT use in these cases, no specific guidelines exist for patients with IBD.

Given its poor prognosis despite surgical and medical intervention, it is reasonable to suggest that increased surveillance and more aggressive treatment may be advisable for patients with IBD. Heightened screening guidelines for CRC have been effective in reducing the stage of diagnosis in IBD patients, as covered earlier in this review, provoking the question of screening for SBA in the future as well. In cases of IBD patients with unresectable duodenal SBA, use of intensity-modulated radiotherapy (IMRT) and strict adjacent small bowel limits of 45 Gy are cautiously advisable.

Prostate cancer (PCa)

There is a significantly increased risk of PCa in men with IBD, with a relative risk of approximately 1.81 (89-92). A large cohort study found that the incidence of PCa in men with IBD at 10 years was 4.4% compared to 0.65% in controls (93). A retrospective study found that men with IBD did not differ in age at diagnosis but were diagnosed with a lower Gleason score (3). Pathological analysis of PCa samples from men with IBD showed a greater incidence of B and T cell infiltration into the tumor compared to samples from men without IBD (94). Studies of chemically induced intestinal inflammation in mice mirrored this finding, and further demonstrated increased DNA damage and pro-oncogenic signaling (94). Inflammation may impact have an early impact on the prostate, resulting in a poor predictive value of traditional diagnostic testing in patient with IBD (95). Additionally, some theorize that the link between IBD and PCa may be the introduction of microorganisms to the prostate creating a pro-oncogenic local microbiome (96).

While IBD patients may present with less advanced PCa, historically their cancer management has been more invasive. 40% of patients with IBD and PCa undergo surgical management compared to just 27% of their peers without IBD, and patients with IBD were significantly less likely to receive radiation therapy (3). Use of androgen deprivation therapy (ADT) was similar between groups (3).

This represents a hesitation to give radiotherapy to patients with IBD due to a perceived increased risk of complications like IBD flares or bowel toxicities like radiation proctitis and rectal bleeding, reflected in the NCCN PCa treatment guidelines rating active inflammatory disease of the rectum as an absolute contraindication to EBRT and inactive UC as a relative contraindication (4-6).

Although the data are limited, studies of conventional EBRT in patients with IBD and PCa revealed increased rates of both acute and late ≥ 3 bowel toxicities (6,97). In a retrospective study of 28 patients with IBD and PCa, 21% experienced toxicities severe enough to warrant cessation of radiotherapy (6). Of the patients who experienced those toxicities, 75% had received conventional EBRT. A systematic review of 8 studies revealed severe acute bowel toxicity rates of 20% in patients with IBD who underwent EBRT, and severe late bowel toxicity rates of 15% (97). Strong conclusions on the safety of EBRT in patients with IBD are limited by the lack of published, well-powered studies.

However, the same review showed improved toxicity rates in those who received low dose rate (LDR) brachytherapy, with severe bowel toxicities rates of 7% and 5% for acute and late respectively (97). Similarly, a study of 24 patients with IBD and PCa who underwent LDR brachytherapy found no grade ≥ 2 rectal toxicities with a median follow up time of 48.5 months (98). A study of 11 patients with IBD and PCa who underwent high dose rate (HDR) brachytherapy revealed no grade ≥ 2 bowel toxicities with a median follow up time of 6 months (99). The culmination of these studies suggests brachytherapy is well tolerated in IBD patients. That being said, biopsies in the recently radiated field, and the placement of LDR implants in patients with active IBD flare are associated with higher rates of toxicities, suggesting HDR may be safer for patients with IBD, and that biopsies to the rectum after brachytherapy should be limited (100).

Fortunately, use of newer RT approaches which minimize radiation to the nearby bowel and rectum, particularly IMRT, may not have significant increases in either IBD flares or radiation toxicities (7,12,13,101). For patients with IBD with PCa, IMRT produces lower rates of acute grade ≥ 2 toxicities than 3D-CRT, indicating that precision techniques may be particularly valuable in the approach to the IBD patient (13). In one study of 18 patients with IBD and PCa, all cases of grade 2 proctitis followed treatment with three-dimensional conformal radiation therapy (3DCRT), with no cases following IMRT or LDR brachytherapy (101). Remarkably,

this study also showed a decrease in grade 1 diarrhea pre-radiation to post-radiation, suggesting that radiation may have alleviated some symptoms of IBD. Ultimately, there is a growing number of articles which suggest that radiation is a viable treatment option for patients with IBD and PCa (7-10,12-14,101).

Moreover, recent publications reported reduced risk of rectal toxicities in patients with IBD with placement of rectal spacers to displace the anterior rectal wall out of the field of radiation (102-105). In a case report, the use of hydrogel spacer in a patient with IBD and PCa treated with IMRT resulted in reduced rectal dose from 78.7 to 60.4 Gy, without and with the hydrogel spacer, respectively, resulting in Grade 1 GI toxicities of mild diarrhea. (102) One center treating 8 patients with IMRT and HDR brachytherapy boost with an injectable hydrogel spacer, with minimal acute toxicities and no late grade ≥ 2 gastrointestinal toxicities in the median 36 month follow up period (105). Similarly, the toxicity profile with the use of biodegradable rectal balloon implants inflated with saline is favorable and can be utilized in both the EBRT and brachytherapy setting (103,104). However, in cases which require radiation to the pelvic lymph nodes, radiation to the bowel is more difficult to avoid.

Overall, patients with IBD have an increased risk of PCa, but with lower Gleason scores at diagnosis. Patients with IBD have increased lymphocytic infiltrate into the prostate, suggesting that chronic inflammation plays a significant role in the early changes and eventual neoplasia of the prostate. While contested, there is data that suggests that conventional EBRT results in higher toxicity rates in IBD patients (6,97). However, there is reasonable evidence to suggest that brachytherapy and IMRT are reasonable management options for PCa patients with a history of IBD. At our own institution, HDR brachytherapy is preferred to IMRT in patients with IBD to avoid toxicities associated with treating the pelvis. There is growing support for the use of implantable spacers to reduce rectal toxicities. These recommendations are summarized in *Table 1*. It is important to have multidisciplinary discussions with surgical and medical oncologists to determine if another mode of treatment would be better tolerated or more in line with the patient's treatment goals and present the patient with all of the reasonable options, including RT, which may be suitable to treat their PCa.

Cancers with no proven association with IBD

Other cancers adjacent to bowel that may warrant

Table 1 Summary of recommendations for IBD patients

Malignancy	Management in sporadic cases	Management recommendations in IBD-associated cases
Colon adenocarcinoma	Segmental resection, concurrent chemotherapy, RT to 45 Gy + boost (106)	TPC with IPAA, concurrent chemotherapy, use of prone positioning and conformational RT
Rectal adenocarcinoma	Early stage: surgery + EBRT + chemotherapy Late stage: preoperative RT + 5-FU, definitive surgical resection, adjuvant chemotherapy (106)	Preferred proton therapy over EBRT (45)
Anal carcinoma	Mitomycin/5-FU + EBRT (50–59 Gy, depending on stage) Fill bladder and utilize prone position to minimize small bowel dose (107)	Utilize multimodality care when possible, including surgery and radiation with or without chemotherapy (46)
Lymphoma	Depends on subtype: Radiation alone for: follicular lymphoma I–II, extranodal MALT IE–IIE, nodal marginal zone lymphoma I–II Combined modality (chemotherapy and IFRT) for: classical HL I–II, advanced HL, diffuse large B-cell lymphoma I–II, peripheral T-cell lymphoma I–II (108)	Limit use of immunosuppressive IBD therapies during treatment
Small bowel adenocarcinoma	Wide resection and lymph node dissection + chemotherapy Duodenal: preoperative chemoradiation for unresectable cases (3D conformational or IMRT) Jejunum/ileum: RT not indicated (109)	Preferred IMRT for unresectable cases
Prostate cancer	Low risk: similar outcomes for radical prostatectomy, EBRT, or brachytherapy Intermediate risk: dose escalation above 70 Gy with short-term ADT High risk: EBRT with long-term ADT (4)	HDR brachytherapy is most preferred, limit biopsies IMRT is preferred to 3DCRT and conventional EBRT (13,101) Utilize implantable perirectal spacers (hydrogels, balloon) (102–105)

IBD, inflammatory bowel disease; RT, radiation therapy; TPC, total proctocolectomy; IPAA, ileal-pouch anal anastomosis; EBRT, external beam radiation therapy; 5-FU, 5-fluorouracil; MALT, mucosa associated lymphoid tissue; HL, Hodgkin lymphoma; HDR, high dose rate; ADT, androgen deprivation therapy; IMRT, intensity-modulated radiotherapy; 3DCRT, three-dimensional conformal radiation therapy.

radiotherapy include cervical/gynecological cancers, bladder/genitourinary cancers, and upper GI/hepatobiliary cancers; however, these cancers have an unclear relationship with IBD. Cervical cancer risk in patients with IBD has been contested, with conflicting results at different centers, as summarized in the study by Hazenberg *et al.* (105). The possibility of increased cervical neoplasia in the IBD population was first established in 1994, pointing to azathioprine treatment as a possible cause (110). The theory of immunosuppressant medications being associated with increased cervical neoplasia was extended to include 6-mercaptopurine (MP), methotrexate, and steroids (105). It is theorized that immunosuppressive agents prevent effective

clearing of HPV, allowing for greater neoplastic potential. It is not consistently accepted that the IBD disease state is associated with cervical cancer; however, some studies have indicated increased rates of abnormal pap smears and dysplasia in patients with IBD with or without HPV (111–113). There are no clear cervical neoplasia prevention, screening, or treatment guidelines specifically for patients with IBD; therefore, it is reasonable to approach these cases with the same guidelines that apply to the general population. There is no established relationship between IBD and vulvar, vaginal, endometrial, or ovarian cancer (105).

IBD and urinary tract cancers also have a debated correlation. A 2010 pooled analysis found a 2.03

standardized incidence ratio (SIR) of bladder cancer in CD patients, but not in UC patients (114). Additional analysis has found the CD bladder cancer risk to be only marginal at an SIR of 1.19 (115-117). Notably, patients with IBD have an increased risk of renal cell carcinoma (RCC); however, they are known to be diagnosed at a younger age with earlier tumor stage and have favorable outcomes compared to the general population (115,118). It is theorized that more frequent imaging of the abdomen may contribute to higher rates of early recognition and incidental findings of renal malignancy in patients with IBD. Immunosuppressive or biologic therapy for IBD is not associated with worse outcomes in RCC patients; however, thiopurines are associated with higher rates of developing kidney and urinary tract cancers and should be avoided in these patients (118-120). No relationship between IBD and male genital cancers has been established (115,117). Given the marginal relationship with IBD and early detection for urinary tract cancers, it is reasonable to approach treatment using the guidelines applicable to the general population, with special attention to IBD therapy choice during treatment.

Although a part of the gastrointestinal tract, upper GI cancers have a complex relationship with IBD. Gastric cancers do not have a proven association with either CD or UC (121). UC, as associated with PSC, is thus associated with an increased risk of cholangiocarcinoma (122). Notably, colectomy did not reduce the risk of cholangiocarcinoma in patients with IBD-PSC. Additionally, some have proposed a broader relationship between IBD and hepatobiliary cancers (73,123,124); however, others have not replicated the findings of increased rates of hepatobiliary cancer in patients with IBD (125). Ultimately it is difficult to discern whether there is an independent relationship between hepatobiliary cancers and IBD, or only an association of PSC and hepatobiliary cancer (126). And notwithstanding that PSC is associated with gallbladder carcinoma, IBD-PSC does not have a known association with gallbladder carcinoma (127). While management should follow the guidelines used in the general population, it is especially important to monitor nutritional and electrolyte status in these patients, as patients with IBD may experience disturbances in oral intake and GI losses at baseline.

Regardless of an established association, spontaneous cancers in proximity to bowel do arise in patients with IBD. Given the unclear relationship, it is difficult to find firm recommendations and data regarding treatment options for IBD patients with incidental malignancies in proximity to bowel. However, we extend some of the

principles established earlier in this review to make the following recommendations when considering RT for IBD patients: assess the severity and location of a patient's IBD, utilize modalities and positioning which limits unnecessary radiation to the neighboring bowel, consult closely with the patient's gastroenterologist to determine whether continuation of immunosuppressive and biologic medications is recommended, coordinate with the medical oncologist and surgical oncologist to determine the safety and prognosis of utilizing medical and surgical alternatives, involve a nutritionist to optimize patient recovery and reduce the effects of bowel toxicity related dehydration or electrolyte disturbances, evaluate the need for additional cancer screening as dictated by the patient's risk factors like IBD duration and history of immunosuppressant use.

IBD during radiation therapy

The presence or history of malignancy warrants special consideration for the management of IBD. It is generally accepted that the approach must be personalized to the patient and consider both the severity of the IBD when inadequately treated, and the risk associated with the diagnosed malignancy. This section will summarize recommendations for the use of IBD therapies during RT, and the concern for IBD flares during this period. Holistic care requires a multidisciplinary approach, incorporating medical oncologists, radiation oncologists, surgeons, gastroenterologists, and nutritionists.

There is a complex interplay of IBD therapies and cancer management- as IBD therapies can impact the development of cancer, and cancer therapies can exacerbate IBD. While there is little high level data to indicate the best therapeutic options for treating IBD during RT, it has been proposed that the use of IBD medication during therapy may predict slightly increased risk for acute GI toxicities in PCa patients (12).

Firstly, we will discuss the use of immunosuppressives, as they may contribute to cancer pathogenesis and poor healing. It is recommended that immunosuppressive agents are held until the malignancy is cured or controlled (14,128,129). Thiopurines, believed to have high oncogenic potential, are stopped or switched to methotrexate (130). A study of colorectal cancer patients undergoing surgical resection demonstrated that patients on immunosuppressive therapies have worse long-term oncologic outcomes, including overall and disease-free survival (131). A French prospective database revealed that patients with IBD are less

likely to receive immunomodulatory agents and are more likely to undergo management of IBD via surgeries (130). Based on this body of information, it is reasonable to suggest that patients should consider discontinuing immunosuppressive medications to optimize their oncologic and RT management. Guidelines specify that should immunosuppressant therapy need to be restarted, it is optimal to wait 5 years to limit cancer recurrence; however, the evidence is empirical (129).

Next, we will discuss the use of biologic agents, as they are frequently utilized in the IBD population, and may have a role in both cancer pathogenesis and cancer death. There is little data available on the use of biologics, including TNF- α inhibitors, during radiation therapy. Most of the literature has assessed oncologic outcomes in RA patients utilizing biologics (129). The role of inflammatory cytokines in IBD and in tumor progression remains a highly debated topic with ongoing investigation. TNF- α is thought to promote malignancies through activation of the COX-2 pathway, inducing DNA damage, and upregulating angiogenesis; and TNF- α inhibition is thought to reduce IBD activity and CRC development (29). However, upregulation of TNF- α is being investigated for its role in promoting radiosensitivity and plays a critical role in apoptosis, raising concern that inhibition of TNF- α may hinder adequate cancer suppression (132,133). There is little clinical data on oncologic outcomes for patients with IBD with malignancy treated with TNF- α inhibitors, but some suggest that 5-year survival may be similar regardless of IBD drug choice (134). European Evidence-Based Consensus guidelines include TNF- α inhibitors as agents to withhold at least until cancer therapy is completed (129). IBD patients with a history of malignancy ultimately spend a similar number of years on steroids and anti-TNF agents compared to their IBD peers without malignancy, indicating that these agents are generally restarted after oncologic management is completed (130). Empiric evidence suggests restarting anti-TNF therapy as early as 3 months post-treatment but it is generally recommended to wait at least 2 years (135-137).

Generally, the preferred IBD management in the setting of malignancy includes 5-aminosalicylic acid, local steroid therapy, nutritional therapy, antibiotics, and surgery as needed (129). Other biologics like vedolizumab and ustekinumab, are generally considered safe; however, there are limited data (14). Nutrition should be specifically discussed with patients with IBD undergoing RT. Many patients with IBD chronically suffer from nutritional

deficiencies and malabsorption. RT to the pelvis has the potential to exacerbate this, and thus should be addressed early in treatment. Moreover, IBD patients with lower BMI may be more likely to suffer flares in the peri-radiation period (44). Nutritional therapy recommendations for both IBD and pelvic radiation disease (PRD) share common management goals, including increased caloric intake, limiting dairy products, lowering fat content, and increasing protein content (138). There is evidence that the introduction of an elemental/oligomeric enteral diet may improve both IBD and PRD (138-140).

Just as IBD medications can impact the disease course of cancer, the management of cancer may also impact IBD course. Cytotoxic therapies may improve IBD status, while hormonal therapies may exacerbate it (141). For RT, attributed toxicities may overlap with the natural disease course of IBD. Symptoms of pain, fecal urgency, fistulation, and obstruction are signs of both active IBD and RT complications. There is disagreement on whether flare-free interval prior to treatment is predictive of subsequent flare following RT (3,9,12). Barnett *et al.* found an increased risk of fecal urgency and loose stools in their IBD arm; although, the risk of proctitis, rectal bleeding, stool frequency, or urinary side effects was not increased compared to controls (142). Another study showed an increased risk of adhesions and small bowel obstruction in the IBD-RT arm; however, comparison to the IBD without RT arm suggests that these complications cannot be attributed to RT (43). In PCa, it is unclear whether D'Amico Risk Group or RT is associated with an increased risk for subsequent flare following treatment (4,10,143). RT does not increase the risk of stricture, fistulation, or subsequent IBD activity/flare in the IBD population (9,15,43). Of note, 61% of patients with IBD treated with RT for various primary malignancies were classified as "in remission" from IBD 6 months after RT, with only 2 patients experiencing severe IBD symptoms during follow-up (9,44).

To sum up the approach to IBD management in coordination with RT, immunosuppressive agents like thiopurines should be minimized and biologics like TNF- α inhibitors should be approached with caution. Also, 5-aminosalicylic acid, local steroid therapy, nutritional therapy, antibiotics, and surgery are preferred. Involving a nutritionist is recommended in minimizing both the effects of IBD and acute radiation toxicities. There are little available data on how IBD therapies impact the outcomes of RT, which represents a promising opportunity for future research.

Conclusions

While historically it was believed that IBD-associated malignancies could not be safely managed with RT due to GI toxicities and IBD flares, updated analysis has refuted this belief. Advancements in precision radiation techniques, and utilization of positioning and spacers, allow for lower doses of radiation to the neighboring bowel and rectum than was previously possible. For each disease site, modifications to the standard of treatment for patients with IBD are summarized in *Table 1*, often making RT a viable treatment modality choice for these patients.

Although there is a substantial body of case reports and small studies on RT in patients with IBD, the power of the data is often lacking. Potential studies with larger power are limited by the infrequency of some cancers, like IBD-associated anal carcinoma. There is a growing body of evidence that patients with IBD fare equally as well as their peers with sporadic malignancies when appropriate RT techniques are utilized (8,9,14-16). The denial of RT to patients with IBD represents a practice based in tradition, rather than in data. Given the critical role RT plays in the management of a number of IBD-associated malignancies, we recommend including RT in the multidisciplinary planning discussions and treatment options presented to the patient.

IBD-associated malignancies are a particularly interesting phenomenon in the greater scheme of understanding the complex relationship between inflammation, cancer pathogenesis, and cancer treatment. While the prolonged state of inflammation in the bowel results in greater incidence of neoplasia (35,69,77,78), even extending into neighboring organs like the prostate (94), many inflammatory markers are associated with cancer cell death and resolution. RT initiates an inflammatory response through the release of alarmins, calreticulin, and type 1 interferon (144-146). While this response is at least partially responsible for clearing the cancer, it is also responsible for the development of some toxicities, like fibrosis (144). This elicits a number of questions relevant to cancer patients with IBD, and on a larger scale, all patients receiving RT. How does the use of anti-cytokine therapies, commonly prescribed to patients with IBD, impact the efficacy of RT? Can systemic anti-inflammatories play a role in reducing radiation toxicities, and can a localized tumor environment high in inflammatory molecules heighten treatment response?

To elucidate the answers to these questions we will

have to overcome the limitations of small sample sizes, difficulty differentiating the natural IBD disease course from true bowel toxicities, and confounding variables like polypharmacy and multiple diagnoses, which are common in patients with auto-inflammatory conditions. Much of the data comes from retrospective data analysis derived from large databases, rather than dedicated IBD-malignancy focused studies. While it is clear that more research is required to fully appreciate the unique course of IBD-associated malignancies, it is also evident that our policies on utilizing RT in this special population must be updated.

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Footnote

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