Rectal Cancer and Radiation in Colitis

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Abstract

Inflammatory bowel disease (IBD) is associated with an increased risk of colorectal cancer. When IBD patients develop a rectal cancer, this should be treated with the same oncological principles and guidelines as the general population. Rectal cancer treatment includes surgery, chemotherapy, and radiation therapy (RT). Many IBD patients will require a total proctocolectomy with an ileal-pouch anal anastomosis (IPAA) and others, restoration of intestinal continuity may not be feasible or advisable. The literature is scarce regarding outcomes of IPAA after RT. In the present review, we will summarize the evidence regarding RT toxicity in IBD patients and review surgical strategies and outcomes of IPAA after RT.

Keywords

- inflammatory bowel disease
- rectal cancer
- ileal pouch-anal anastomosis
- radiation therapy
- functional outcomes

The reported risk for colorectal cancer (CRC) in inflammatory bowel disease (IBD) patients compared with the general population varies widely. Epidemiological studies have reported from small/no additional risk[1] to up to 4.5 times higher.[2] Most of the literature indicates that the risk of CRC in IBD patients is approximately 1.5 to 2.0 times greater than in the regular population.[3] Chronic inflammation likely drives the neoplastic process. Although the genes involved in the carcinogenic process are the same as in sporadic cancers, the sequence in which they mutate in IBD-associated CRC is different, with an early inactivation of *p53* and late mutation in the *APC* gene.[4]

Irrespective of this difference in the order in which genes mutate, the treatment for rectal cancer in the context of IBD follows the same principles as in the general population, including a multimodal approach with chemotherapy, radiation therapy (RT), and surgery. Of course, an additional layer of complexity is present in IBD patients, especially in cases where total proctocolectomy (TPC) and ileal pouch-anal anastomosis (IPAA) is the best oncologic option and the only option to restore intestinal continuity. There is a notion that IBD is a relative/absolute contraindication for RT, and we will discuss the available literature on this topic.

In the present review, we will review the mechanisms of toxicity of RT in the bowel, rectal cancer management in the context of IBD, and surgical options and outcomes of IPAA and RT.

Radiation Therapy in IBD: Toxicity and Disease Activity

RT toxicity is caused by direct damage to the DNA of the normal tissue surrounding the tumor. As a result of the indirect ionization of water, RT produces free radicals, most notably hydroxyl radicals. These radicals can cause cell cycle arrest, apoptosis, and eventually tissue necrosis due to impairment of the DNA repair via the *p53* pathway.[5]

The bowel epithelium has a high proliferative rate, making it very susceptible to injury from RT. The primary effect of RT is on mucosal stem cells within the crypts, not only causing direct damage to the stem cells, but also resulting in microvascular injury and fibrosis.[6] The cellular reserve of the intestinal villi is then depleted, resulting in shortened villi with mucosal denudation, edema, inflammation, and decreased absorptive area. Within hours of exposure, histological evidence of RT-induced injury can be seen: leukocytes infiltrate crypts, followed by abscess formation 2 to 4 weeks later. Ulceration might be present at this time. A gradual occlusive vasculitis, foam cell invasion of the intima, hyaline thickening of the arteriolar walls, collagen deposition, and

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fibrosis, frequently in the submucosal layer, are some of the subsequent alterations.[7]

Because of these microscopic changes, the bowel wall becomes thicker due to fibrosis and the small arterioles are obliterated causing ischemia. The lymphatic drainage is also altered, worsening the inflammation and edema. The mucosa also becomes atrophic, with atypical hyperplastic glands. In addition to fibrosis of the vessels leading to ischemia, blood vessels can degenerate into telangiectasias and cause bleeding. The mucosal ulcers can perforate, fistulize, or form abscesses. As the inflammation heals, fibrosis can narrow the intestinal lumen forming strictures that can eventually lead to obstruction.

These mucosal changes can impair absorption of nutrients, vitamins, and bile salts, leading to dehydration, electrolyte imbalances, and protein loss.[8] RT also alters gut motility.[9] The colon and rectum seem to be less affected by RT toxicity when compared with the small bowel. When the colon and rectum are compromised, the inflammatory process can mimic IBD.

Unfortunately, there are no large-scale prospective studies examining the toxicities of abdominopelvic irradiation in patients with IBD. This is likely because IBD has a relatively low incidence rate (0–192 per million for ulcerative colitis [UC] and 0–202 per million for Crohn's disease [CD] in North America), and RT has often been avoided in this population for a fear of complicaitons.[10] Most of the research that is currently available consists of retrospective series or systematic reviews spanning long periods of time. These studies often do not take into account more modern radiation modalities that may have different outcomes, such as intensity-modulated radiation therapy (IMRT). Furthermore, studies group together patients receiving different RT modalities such as external beam radiation and brachytherapy and with different radiation indications and doses, i.e., rectal cancer, anal cancer, prostate cancer, and gynecological cancer.

While some studies describe a higher RT toxicity in IBD patients, others do not. In a retrospective study with 161 patients with IBD and rectal cancer, 66 (41%) received preoperative therapy, chemoradiation (CRT), short-course RT, or long-course RT.[11] The rate of grade 3 acute toxicity was highest in CRT patients (28.6%), which is greater than expected among non-IBD patients. Interestingly, 28.1% of patients experienced grade 3 complications within 30 days of surgery, but the kind of preoperative therapy had no bearing on this high rate of complications. Another cohort composed of IBD patients showed that newer techniques, such as IMRT, resulted in lower rates of adverse events, both acute and late onset.[12] Grade 2 toxicity was reported in 28% of IMRT patients compared with 100% of 3D-CRT patients ($p = 0.01$). On the contrary, greater rates of RT-related toxicity in IBD patients were not found in a retrospective investigation of 186 patients with rectal cancer. Three groups made up the sample: 71 patients with IBD who underwent RT, 71 matched controls without IBD, and 44 nonmatched controls with IBD treated without RT.[13] Patients with and without IBD had similar number of RT interruptions or use of antidiarrheal medication. Also, the rate of complications in the long term was similar between the IBD patients who underwent RT and the nonmatched cohort of IBD patients treated without RT. No differences were found in other acute or long-term toxic effects.

A 2019 meta-analysis that included 8 studies with 204 IBD patients undergoing RT calculated the rate of acute grade 3–5 toxicity as 14% (7–22.4) and late grade 3–5 toxicity as 10.2% (3.2–19.7).[14] A more recent systematic review that included 19 studies and 497 patients (50.5% with UC) with rectal and anal cancers reported range for acute $\geq$grade 3 toxicity to be 0 to 28% and for late grade 3 or higher toxicity to be 0 to 13%.[15] To put these numbers into perspective, the incidence of grade 3 or higher gastrointestinal (GI) toxicity for prostate cancer irradiation in non-IBD patients has been reported to be 0.6 to 0.8% in the early setting and 2.6 to 4.1% for late sequelae.[16] For anal cancer patients, these numbers are 36 to 46% for early toxicity and 2.5 to 3% for late toxicity.[17] For patients with rectal cancer without IBD, grade 3 GI toxicity occurs in approximately 14% of cases.[18] Studies reporting toxicity on IBD patients after RT are summarized in ►**Table 1**.

There is little evidence available about how RT affects IBD activity after therapy is complete. In a retrospective study with 84 IBD patients receiving RT for prostate cancer, active IBD treatment during RT was found to be a predictor of acute >grade 2 toxicity (57 vs 7%; $p = 0.03$), but the flare-free period before exposure to RT was not proven to be a predictor of later flare.[19]

Two larger studies also addressed the rates of IBD flares requiring escalation of treatment in the year following RT.[20,21] Kirk et al examined 240 men who were being treated in the Department of Veterans Affairs (VA) system for prostate cancer and IBD at the time of their cancer diagnosis.[20] With a flare rate of approximately 18% among patients with IBD and prostate cancer, there was no statistically significant difference in the number of flares that occurred in the year after treatment between groups receiving active surveillance/androgen restriction therapy, RT alone, and surgery alone. The presence of a flare in the year before therapy (odds ratio, 12.5; 95% confidence interval [CI], 5.4–29.2) was the sole factor that predicted a flare after therapy ($p < 0.001$).[20] Another study examined a comparable demographic in four VA medical centers in Texas and Virginia.[21] One hundred individuals with prostate cancer with IBD (29% CD, 66% UC, and the remaining with indeterminate colitis) were included in this study. The RT group and those receiving other treatments did not differ statistically in terms of age, race, IBD type, or stage of cancer. Univariate analysis revealed no statistically significant differences in the number of IBD flares, hospitalizations for IBD, or procedures related to IBD that occurred after therapy. However, on multivariate analysis, RT was identified as a risk factor for subsequent IBD flare.[21]

Annede et al reported on 28 patients with various malignancies treated in France.[22] In this study, the severity of IBD was assessed using the Harvey Bradshaw Index and the Mayo Index for CD and UC, respectively. Within the first 6 months following treatment, 50% of patients were in remission and this improved to 61% at 6 months. Only two patients experienced

Table 1 Studies reporting toxicity of RT in IBD patients

Author (year)	*n*	IBD	Primary malignancy	RT modality	Mean dose (cGy)	Toxicity grade ≥ 3 (%)	
						Acute	Late
Green et al[66] (1999)	15	NR	Rectal	EBRT	5,040	20	13
Willet et al[67] (2000)	28	CD 10/UC 18	17 CRC, 7 prostate, 4 other	EBRT	4,010–5,110	21	29
Song et al[68] (2001)	24	CD 15/UC 7	17 abdomen/pelvis, 8 chest	EBRT	4,500	21	8
Peters et al[69] (2006)	24	CD 7/UC 17	Prostate	BT 21, BT + EBRT 3	4,500 (EBRT)	0	0
Glick et al[70] (2014)	61	CD 30/UC 28	18 anal, 17 rectal, 17 prostate, 9 other	EBRT	NR	11	NR
White et al[12] (2015)	19	CD 5/UC 14	8 prostate, 5 upper GI, 3 rectal/anal, 3 liver	EBRT	5,400	11	5
Chang et al[71] (2015)	15	CD 4/UC 8, not specified 3	14 CRC, 1 anal	EBRT	4,500–5,400	27	13
Rhome et al[72] (2015)	42	CD 22/UC 20	Prostate, rectal, anal, colon, other	EBRT/BT	5,040	23	NR
Gestaut and Swanson[73] (2017)	18	CD 2/UC 16	Prostate	EBRT/BT	7,020 (EBRT)	0	0
Annede et al[22] (2017)	28	CD 13/UC 15	Prostate 12, rectal 8, cervix 5, anal 2, endometrial 1	EBRT/BT	5,300	11 (GI specific)	4 (GI specific)
Bosch et al[11] (2017)	66	CD 30/UC 33/not specified 3	Rectal	EBRT	2,500–5,000	0–28.6	NR

Abbreviations: CT, brachytherapy; CD, Crohn's disease; cGy, centigray; CRC, colorectal cancer; EBRT, external beam radiation therapy; GI, gastrointestinal; IBD, inflammatory bowel disease; NR, not reported; RT, radiation therapy; UC, ulcerative colitis.

severe IBD symptoms in follow-up, both of which were patients with prostate cancer (both treated with high doses of RT).

Despite the scant evidence, RT appears to have minimal or no impact on the intensity or activity of IBD. The most accurate technique to predict the likelihood of a flare after RT is probably to know how active or well controlled a patient's IBD is before starting treatment.[15]

Rectal Cancer and IBD

The potential influence of IBD on the natural history and prognosis of CRC has not been fully elucidated. No prospective studies have compared the survival of patients with CRC by the presence of IBD, and the available retrospective studies have yielded contradictory findings. Two population-based studies from Denmark have compared UC and CD specifically regarding survival compared with patients without IBD. In the UC study, 279 UC colorectal cases were compared with 71,259 sporadic non-IBD cases; cancer stage, rates of lymph node, and distant metastases were similar, but overall mortality at 1 and 5 years was higher in the UC group.[23] Similarly, when 100 CD CRC cases were compared with 71,435 sporadic non-IBD cases, the hazard ratios (HRs) for death at 1 and 5 years were both increased in patients with CD.[24] A meta-analysis of 12 studies with a total of 3,472 patients with IBD and CRC described a 24% higher risk of death (HR, 1.24; 95% CI, 1.19–1.29) in patients with IBD than in patients without IBD.[25] However, in a large multicenter study of 371 patients who had IBD with CRC compared with 52,243 patients who did not have IBD with CRC, IBD status did not significantly influence overall survival.[26] On the other hand, other large multicenter and population-based studies[27–29] have reported a trend of significant decrease in overall survival in patients with IBD who had CRC in comparison with patients without IBD, even when matched by age, sex, and stage at diagnosis.[27]

Regarding rectal cancer, the literature is scarce. We know that IBD-associated rectal cancer presents at earlier stages (I or II), and a significant proportion is an incidental pathology finding.[30,31] Overall survival for these patients after surgical treatment has been reported to be between 95.8 and 62%.[30–32] In a recent report, 107 patients with IBD who have rectal cancer were matched to 215 control rectal cancer patients. The overall survival rates in patients with IBD and without IBD at 3 years were 73 and 83% and at 5 years were 70 and 75%, respectively. The disease-free survival rates at 3 years were 62 and 75% and at 5 years were 56 and 70%, respectively, but differences were not statistically significant.[33] Of note, patients with IBD received less chemotherapy and had a higher proportion of positive circumferential margin. Considering these numbers, it is fair to assume that patients with IBD-associated rectal cancer have a similar prognosis compared with regular cancer patients.

Surgical Considerations

Patients with IBD and rectal cancer should be discussed in a multidisciplinary meeting, and when surgery is indicated,

they should undergo a proper oncological operation following the principles of total mesorectal excision (TME). Despite retrospective series describing metachronous cancers in up to 40% of the cases,[34] when an IBD patients presents with an invasive CRC, the extent of surgical resection is not specified by guidelines.[35–37] Clearly, a TPC removes the residual colon and the possibility of developing a second primary CRC. This approach, however, is complicated by the risk of local recurrence and metastatic disease, and the implications of undergoing future treatment with either an IPAA or an end ileostomy. Estimating the true risk of metachronous primaries in the colon has been the topic of multiple retrospective studies, and clearly differs between IBD subtypes.

The use of segmental resection in elderly UC patients (median age, 73) was examined by Khan et al. They found that no patients who underwent segmental resection in their 7-year follow-up developed a metachronous cancer, suggesting that segmental resection is safe in the elderly UC population.[38] Another single-center study suggested that segmental resection with intensive surveillance in IBD is feasible as recurrent dysplasia can be identified early resulting in a subsequent intervention, with better quality of life.[39] Furthermore, a recent retrospective study from Canada with 83,729 patients who underwent surgery for CRC, 965 of them with IBD, showed no difference in overall survival of segmental resection versus proctocolectomy at 6 months and 1, 3, and 5 years of follow-up.[40] Especially in a cancer population, where future therapies may be necessary for local pelvic recurrence or distant metastatic disease, the theoretical risks of segmental colectomy/proctectomy have to be weighed against the ability of patients to tolerate additional therapies with an IPAA or end ileostomy.

Historically, while UC-associated cancer has been a clear-cut indication for TPC, this was not the case for cancer in Crohn's colitis given its segmental nature. In a widely cited study from the Mount Sinai Hospital in New York, Maser et al suggested that proctocolectomy should be considered in CD-associated CRC patients after demonstrating that 39% of them developed metachronous cancers after segmental and subtotal colectomy, and 50% of these patients died from this metachronous disease.[34]

Another population-based study using the Ontario Cancer Registry revealed that IBD-associated CRC has worse overall survival than sporadic CRC, especially in young patients and those with stage III disease, whereas those with stage I disease have better survival than those with sporadic CRC.[40] These factors need to be considered when discussing the extent of the operation proposed. Younger patients with earlier stages are expected to have longer survival times, with a subsequent higher risk of metachronous cancer, and would benefit from a more radical risk-reducing operation. On the other hand, in patients at high risk for recurrence/metastases, or those with a shorter life expectancy, segmental resection may be appropriate.

Clearly, if the whole colon and rectum are resected, the only option to restore intestinal continuity is an IPAA. Patients with IBD and rectal cancer might be candidates for IPAA.[30] If RT is indicated, it should be performed preoperatively, which will be addressed more thoroughly in the next section.[41,42] Absolute contraindications to IPAA are poor sphincter function, tumor involvement of the anal sphincter requiring an abdominoperineal resection, and active acute inflammation due to the high risk of pelvic bleeding, pelvic nerve injury, and postoperative complications/pelvic sepsis.[43,44]

Ideally, surgery should be performed in high-volume centers to optimize long-term results and reduce the failure rate,[45] which is 4.3% (95% CI, 3.5–6.3) at 5 years.[46,47] Age is not a contraindication for IPAA; nevertheless, functional results and their impact in the patient's quality of life as well as the potential complications should be clearly discussed. The final decision will be made by the patient.

The two main techniques to perform an IPAA are double-stapled anastomosis (DSA) and mucosectomy followed by handsewn anastomosis (MHSA). DSA is accomplished by anastomosing a residual rectal cuff with the ileal pouch with a mechanical circular stapler. In this technique, a residuum of the rectum is left behind. Mucosectomy is the excision of all rectal mucosa with the preservation of 1 to 2 cm of rectal wall to use for subsequent handsewn anastomosis. With this approach, no rectal mucosa is left, but this results in a lower anastomosis. Current guidelines advise use of the DSA technique when possible due to the marginally better functional outcomes, with the specification that the rectal cuff be of no more than 2 cm to minimize the risk of cuffitis and the emergence of new cancers. Except for nocturnal incontinence, which appears to be worsened by mucosectomy, MHSA nevertheless yields results that are comparable to those of stapled anastomosis in most reports.[48]

There is no evidence to favor one approach over the other, and oncologic outcomes are similar. In fact, malignancies can still develop after a mucosectomy.[49] In summary, quality data do not favor either approach; despite this, specialists favor mucosectomy in the case of low rectal cancer.[50]

Feasibility and Advisability of Radiation in Rectal Cancer in IBD Patients

As previously stated, there are no tailored guidelines for rectal cancer in IBD patients. In the United States, according to the National Comprehensive Cancer Network (NCCN) guidelines, early rectal cancers T1/2, N0 should be treated with surgery upfront. This is the ideal scenario for an UC-associated rectal cancer patient who is a candidate for an IPAA and wants to proceed with that. On the other hand, when the tumor infiltrates the mesorectum (cT3) or had suspicious lymphadenopathy (cN+), a multimodal approach with neoadjuvant chemotherapy and radiation is advised, and this can be problematic when an ileal pouch is to be offered.[51]

Following the Mercury trial in the United Kingdom,[52] the European Society for Medical Oncology (ESMO) guidelines recommend TME as the first approach for "low-risk T3 rectal tumors" (no extramural vascular invasion, no compromise of the mesorectal fascia).[53] High-quality magnetic resonance imaging (MRI) is fundamental to select these "good T3"

tumors. With this approach, a local recurrence rate of 2 to 3% has been reported. These results are also supported by two prospective phase II studies from Germany and Canada with similar results.[54,55] In the context of IBD, when a patient is a candidate for an IPAA, this approach is especially interesting considering the interest in maximizing sphincter function.

The use of neoadjuvant CRT or total neoadjuvant treatment poses an extra challenge. We know now that up to 60% of the locally advanced sporadic rectal cancers will develop a complete clinical response and could be candidates for a watch-and-wait approach with no immediate surgery.[56] Little is known about tumor response in the context of IBD.[4] However, assuming that a complete clinical response is achieved, patients might inquire and even opt for a nonoperative strategy for which we have no information and could be potentially harmful in the context of IBD. Having surgery first eliminates this potential scenario.

Functional Outcomes of IPAA after Radiation Therapy

The literature about pelvic radiation and ileal pouches outcomes is primarily retrospective, sometimes multicentric, with small numbers of patients and frequently groups together patients that received radiation for different pelvic cancers, with different doses and radiation fields. Furthermore, to accrue a significant number of patients, these series include patients over long time periods in which the RT technology evolved, and the quality and intensity of the received radiation was also modified.

Neoadjuvant RT may be deleterious to sphincter function, especially when combined with a low-lying anastomosis.[57] Irradiated sphincters suffer from collagen deposition and myenteric plexus damage.[58,59] Even when combined with intersphincteric resection, RT seems to be the primary factor involved in poor bowel function.[60]

In a 2013 retrospective single-center series of 63 patients undergoing IPAA for colitis-associated CRC that included 26 patients with rectal cancer and 11 patients with previous pelvic irradiation, pouch failure occurred in 44% of the irradiated IPAA and 42% of those irradiated for rectal cancer. Although patients with pelvic irradiation presented higher American Society of Anesthesiologists Physical Status Classification (ASA) scores and more advanced disease, in the Kaplan–Meier analysis, previous pelvic irradiation was associated with pouch failure. The mean follow-up was 66 months and the mean time for pouch failure was 54 months.[42] The authors also presented a brief literature review and identified a total of 10 cases of IPAA with pelvic irradiation who had a pouch failure rate of 70%.[42]

The small bowel is a very radiosensitive organ, and irradiation of an IPAA is problematic.[61] A recent multicentric study from Italy and United States with 19 IPAA that underwent external beam RT before ($n = 12$, 63%) or after ($n = 7$, 37%) IPAA showed that the first group presented a significant deterioration of the bowel function during and after RT, with 80% of the patients using pads and presenting night incontinence. In the patients that had an IPAA after pelvic radiation, at a median follow-up of 25 months, bowel function was good, with a median of 5 (range: 4–8) daytime bowel movements, 1 (range: 0–5) night-time bowel movement, and no daytime incontinence and only 1 patient used pads.[62] In contrast with the aforementioned study, with a mean follow-up of 2.5 years the pouch failure rate was 5%. The authors speculated that these better outcomes than reported by others could be due to a shorter follow-up.

It is also known that perioperative complications are associated with worse pouch function.[63,64] In the aforementioned study by Wu et al, pelvic abscess formation was also associated with pouch failure.[42] Given the deleterious effect of RT on wound healing, it is expected to see more postoperative complications when radiation is involved. However, in a recent retrospective analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database that analyzed 3,172 IPAA patients, 167 of whom received pelvic radiation, there were similar 30-day complication rates. This finding remained true when analyzing 596 patients with cancer diagnosis. Curiously, radiated patients presented significantly lower rates of postoperative sepsis, even after controlling for multiple variables.[65] The authors acknowledged the limitations of the database and reflected on the fact that there could be variables not captured in NSQIP that contributed to this counterintuitive finding. Notably, irradiated patients had better scores in the Iowa Rectal Surgery Risk model (a validated model developed to predict postoperative morbidity after proctectomy). Nevertheless, this information is useful to conclude that the deterioration in pouch function in radiated patients does not seem to be related to postoperative complications.

Conclusions

Since there are no specific guidelines for IBD patients with rectal cancer, these cases should be discussed in dedicated tumor boards and managed according to the accepted oncological principles. RT does not seem to be associated with worse toxicity in IBD patients compared with the general population and does not seem to alter the course of the disease.

Patients with IBD-associated rectal cancer seem to have similar survival compared with sporadic rectal cancer patients.

Even though recent studies with limited follow-up time have shown that IPAA following RT has good functional outcomes and low pouch failure rates, care is still advised in these situations because others with longer follow-up have shown considerable pouch failure rates. RT after IPAA should be avoided.

Conflict of Interest
None declared.

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