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Long term clinical toxicity of radiation therapy in prostate cancer patients with Inflammatory Bowel Disease

*Matthew M. Gestaut**, *Gregory P. Swanson*

Department of Radiation Oncology, Scott and White Memorial Hospital, Texas A&M University School of Medicine, Temple, TX 76508, USA

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ABSTRACT

Aim: The study's aim was to examine the clinical impact of radiation therapy (RT) on GI toxicity in Inflammatory Bowel Disease (IBD) patients.
Background: IBD has long been considered a risk factor for increased bowel toxicity from RT; however, minimal evidence exists on patients with prostate cancer (PC) and IBD.
Materials and methods: The tumor registry was queried for patients with IBD and PC from the years 1990–2013. A retrospective review was conducted for patients who received RT. Radiation treatment and toxicity data were collected.
Results: Average length of follow-up was 12 years (median 9.54, range 0.42–19.9). The majority had well controlled baseline bowel function on medical management. Prior to radiation, 60% of patients (9/15) and 40% (6/15) reported grade 0 (G0) and grade (G1) diarrhea at baseline, respectively. No baseline proctitis existed. Following radiation treatment, 78% (14/18) of patients experienced G0 diarrhea while 22% (4/18) reported G1 diarrhea. No patients suffered from greater than G1 diarrhea. Sixty-six percent (12/18), 17% (3/18) and 17% (3/18) of patients experienced G0, G1, and G2 proctitis, respectively. No patients suffered post-radiation stricture formation, and all patients with G2 proctitis received 3dCRT.
Conclusions: Limited published data is available exploring RT for patients with PC and IBD. This analysis offers valuable insight into appropriate counseling for a rare patient subset. Radiation improved late G1 diarrhea rates. Grade 2 proctitis was only encountered in 3dCRT patients. No post-radiation complications occurred. Our findings suggest that IBD patients experience minimal toxicity in the era of IMRT based RT.

1. Background

Inflammatory Bowel Disease (IBD) is a chronic inflammatory process of the gastrointestinal (GI) tract which currently affects approximately 1.3 million patients in the United States.[1] The disease is associated with reduction in quality of life and other comorbidities, such as increased risk of secondary malignancies.[2] Medical management can decrease flare rates of the disease; however, complete remission is

* *Corresponding author at*: Department of Radiation Oncology, 2401 S. 31st Street, Temple, TX 76508, USA. Fax: +1 254 724 8061.
E-mail address: mgestaut@sw.org (M.M. Gestaut).
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uncommon.[3,4] As a result, IBD is considered a chronic disease that patients must live with for the duration of their lives. Due to population aging, more patients are carrying a diagnosis of IBD prior to the initiation of cancer treatment.[5,6]

IBD patients generally suffer from worsened baseline bowel functioning, and there has been considerable concern over the acute and late effects cancer treatment can pose to this subset.[7] Particularly, this has been a topic of debate concerning the effects of radiation therapies on these patients.[8,9] Previously published retrospective reviews have demonstrated mixed results, with some studies reporting increased toxicity rates for radiation therapy and others finding little to no change compared to non-IBD patients.[8–13] Due to the severity of toxicity when it did occur, these studies have generally recommended avoidance of radiation. These analyses are limited, however, by small total patient numbers and high heterogeneity of patients in terms of sites and types of cancer grouped into a single analysis.

Prostate cancer is paramount when considering acute and late GI effects of radiation. No other cancer site utilizes the high absolute total doses (>75 Gy) that have been standardized in prostate cancer. Dose escalation has also been proven to yield a higher biochemical control rate.[14,15] Clinical responses for low and intermediate risk disease appear equivalent for primary surgical management versus radiation therapy. Therefore, both are appropriate treatment regimens.[16,17] Historically, fear of increased GI toxicity secondary to close proximity of the rectum and prostate dictated treatment modality. Patients with IBD were more likely to be referred for surgery than for definitive radiation therapy.[8–10] Thus, treatment options were limited for IBD patients presenting with concomitant prostate cancer. Unfortunately, partly due to the paucity of the two diseases occurring together, these management decisions have been based upon assumptions rather than published evidence. To date, there is limited data available for prostate cancer patients with IBD who were treated with definitive radiation therapy other than several reviews of patients treated with low-dose rate (LDR) brachytherapy and one retrospective review of 16 patients treated with external beam.[11,12,15,16]

2. Aim

The aim of our study is to elucidate the clinical impact of radiation therapy on GI toxicity in Inflammatory Bowel Disease patients.

3. Material and methods

Institutional review board approval was obtained prior to conducting a retrospective patient review and the study was conducted in accordance with the ethical standards of the committee on human experimentation. The tumor registry was queried for individuals who held the International Statistical Classification of Diseases, 9th Revision (ICD9) codes for both IBD and prostate cancer between January 1990 and December 2013. Only patients who were diagnosed with non-metastatic prostate cancer and concomitant IBD were included in the study. In addition, patients treated first with surgery and then salvage radiation therapy for biochemical recurrence were also excluded. Patients were also excluded if they were currently having an active flare of IBD. Only patients in remission or currently on medical maintenance therapy for IBD were included in the analysis. Radiation treatment data collected in the present study includes: Intensity Modulated Radiation (IMRT), 3d Conformal Radiation Therapy (3dCRT), brachytherapy, radiation doses, doses received by the rectum/small bowel, and inclusion of the lymphatic system. Pathologic characteristics of the tumor, including clinical stage, pre-treatment prostate specific antigen, and Gleason score, were also examined.

Baseline characteristics for bowel function were recorded. As show in Table 1, Common Terminology Criteria for Adverse Events version 4 (CTCAE v4) scoring criteria were used to code proctitis/diarrhea baseline, acute and late effects.[17] Acute and late effects were defined as within 3 months of treatment and more than 3 month after treatment, respectively. Follow-up was measured from the date radiation was received to the date of last contact. IBD diagnosis and treatment specifics were also noted, including suppressive medication regimen and active vs. dormant disease.

4. Results

4.1. *Patients*

Initial query of the tumor registry revealed that 166 patients carried the diagnosis of IBD and prostate cancer. All 166 charts were reviewed, with only 18 patients meeting the inclusion criteria for IBD diagnoses and prostate cancer treated with radiation therapy. In patients who underwent surgery, the primary reason cited for offering surgery instead of radiation was the concomitant diagnosis of IBD and fear of increased complication rates with radiation. Average length of follow-up for patients meeting inclusion criteria was 12.0 years (median 9.5, range 0.42–19.9). Of these patients, sixteen patients carried the diagnosis of ulcerative colitis, and 2 held the diagnosis of Crohn's disease. Demographic and other patient characteristics may be viewed in Table 2.

4.2. *Baseline bowel functioning*

For the majority of patients, baseline bowel function was well-controlled with medical management prior to treatment. Twenty-two percent were in remission from IBD without receiving any form of treatment. Fifty-six percent of patients were actively taking 5-ASA; 17% were prescribed prednisone; and 5% were taking Remicade. Three patients had no baseline bowel function data available in the chart. Of patients with available pre-treatment bowel function data, sixty percent of patients (9/15) reported grade 0 (G0) diarrhea at baseline prior to radiation therapy. Forty percent of patients (6/15) suffered grade 1(G1) diarrhea at baseline. No baseline proctitis was present. Two patients had ostomy placed prior to the diagnosis of prostate cancer.

Table 1 – Diarrhea and proctitis CTCAE v4 grading criterion.[20]

Adverse event	Grade toxicity					
	0	1	2	3	4	5
Diarrhea	No change	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Proctitis	No change	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Table 2 – Patient demographic and treatment specifics.

Age	Type of IBD	Medication at time of RT	Completed RT	Prostate dose (Gy)	IMRT or 3DCRT
67	UC	5-ASA	1993	N/A	3DCRT
75	UC	Remicade	2003	N/A	3DCRT
78	UC	5-ASA	2002	144	LDR
72	UC	5-ASA	1992	69	3DCRT
62	UC	5-ASA	2010	N/A	IMRT
65	UC	None	2006	70.2	IMRT
73	UC	5-ASA	2005	66.4	3DCRT
65	UC	5-ASA	1994	65	3DCRT
65	Crohn's	Prednisone	2005	N/A	IMRT
76	UC	Prednisone	2013	74 Gy	IMRT
72	UC	5-ASA	1993	144	LDR
78	UC	None	2007	76.00	IMRT
59	UC	5-ASA	2006	100	LDR
62	Crohn's	5-ASA	1990	N/A	3DCRT
69	UC	None	2000	144	LDR
78	UC	Prednisone	2007	110	LDR
72	UC	None	2002	144	LDR
58	UC	5-ASA	2013	79.20	IMRT

4.3. *Radiation treatment*

Twelve patients were treated with external beam radiation therapy (EBRT), while 6 were treated with low-dose rate brachytherapy. Six patients received 3dCRT; 6 received IMRT. Complete radiation dosimetric records were not available for the majority of patients. Radiation doses were known in 7/12 EBRT patients. Prostate radiation doses ranged from 69.0–79.2 Gy (mean 70.9, median 70.2). For 3 patients, the lymphatics were covered with doses of 45 Gy, 50.4 Gy, and 54 Gy. Brachytherapy was administered in 6 patients as a monotherapy with I-125 144 Gy in 4 patients, and Pd-103 to 100–110 Gy in 2 patients.

4.4. *Toxicity*

During the acute side effect time period, only 9 patients had available data concerning GI toxicity. Three patients suffered from acute G0 diarrhea, 3 patients suffered from acute G1 diarrhea, and 3 patients suffered from acute G2 diarrhea.

Table 3 – Diarrhea at baseline and after radiation treatment.

Diarrhea	Baseline	Post-radiation
Grade 0	60% (9/15)	78% (14/18)
Grade 1	40% (6/15)	22% (4/18)
Grade 2	0	0

Following radiation treatment, 78% (14/18) of patients experienced G0 diarrhea, while 22% (4/18) reported G1 diarrhea. As show in Table 3, no patients suffered from greater than G1 diarrhea. As outlined in Table 4, Sixty-six percent (12/18),

Table 4 – Proctitis at baseline and after radiation treatment.

Proctitis	Baseline	Post-radiation
Grade 0	0	66% (12/18)
Grade 1	0	17% (3/18)
Grade 2	0	17% (3/18)

17% (3/18) and 17% (3/18) of patients experienced G0, G1, and G2 proctitis, respectively. No patients suffered post-radiation stricture formation. All patients with G2 proctitis following radiation treatment received 3dCRT. All cases of grade 2 proctitis resolved within 5 years of treatment with 5-ASA therapy.

5. Discussion

The present study is the second one to report the impact of radiation therapy on GI toxicity among patients with prostate cancer and IBD treated with EBRT. Although patient numbers are low, this retrospective review offers valuable insight into appropriate treatment of this rare clinical subset. Remarkably low GI toxicity existed among the patients in this study. Half of the EBRT patients were treated with now-outdated 3dCRT. Yet, even with outdated means of radiation therapy delivery, Grade 1 diarrhea decreased from 40% at pre-treatment to only 22% at post-treatment.

In other words, radiation appeared to decrease diarrhea caused by IBD. This finding is interesting considering the immunological mechanism of IBD and the known immunological effects of low dose radiation on normal tissue.[21,22] Hematologic and immune cells are exquisitely sensitive to the cytotoxic effects of radiation. Radiation therapy has also been shown to decrease inflammatory cell response in low doses.[23] In addition, the present study found no stricture formations or ostomy placements after radiation therapy. The absence of late complications in this study suggests that anecdotal fears of stricture rate increases are unfounded. The natural progression of the disease may be a more likely explanation for these effects than radiation-related toxicities.

The increase in Grade 2 proctitis was concerning; however, a review of records revealed that the only parameter that differed was the technological type of radiation delivery. Three dimensional conformal radiation was employed for all patients suffering from Grade 2 proctitis. IMRT and image guidance are now the standard of care for prostate cancer treatment, due in part to proven decreases in acute and late effects and higher attainable doses for normal tissue dose constraints.[24–28] Nonetheless, Grade 2 toxicity among these patients was only 17%. In summary, these findings suggest that in the era of IMRT, patients with IBD not only experience minimal toxicity with radiation therapy, but also may experience some relief from symptoms of IBD.

Song et al.[13] identified 24 patients with IBD who underwent radiation therapy at a variety of primary malignant sites. Twenty-one percent (5/24) of these patients developed acute ≥grade 3 toxicity. Only 1 of these patients carried the diagnosis of prostate cancer and he developed grade 4 acute toxicity requiring surgery. This patient was concurrently on the known radio-sensitizer Adriamycin. Eight percent (2/24) of the cohort developed late ≥grade 3 toxicity. The use of concurrent chemotherapy was the only significant factor shared by all patients who suffered from acute and/or late ≥grade 3 toxicity. As reflected by our zero percent grade 3 toxicity rates, the current study did not include patients on concurrent chemotherapy. Concurrent chemotherapy is also not routinely used in the definitive treatment of prostate cancer.

Pai et al.[12] retrospectively reviewed 13 patients who carried the diagnosis of IBD and were treated for prostate cancer with I-125 LDR monotherapy. Fifteen percent of the cohort experienced ≥grade 3 late toxicity. All of the patients who suffered from these late toxicities underwent rectal biopsies within 3 months of implant. Rectal biopsies in a recently radiated field were likely to lead to the increased late toxicities. They also noted that 2 patients with active disease IBD flare while undergoing implant required major surgical correction due to toxicity. This data supports the careful use of LDR monotherapy in selected IBD patients without active disease. It also warns against the use of rectal biopsy in close proximity to the radiation treatment. The current study did not have any post-radiation treatment rectal biopsies completed, nor did any grade 3 toxicities occur.

Murphy et al.[11] is the only other report of external beam radiation therapy in prostate cancer patients with IBD. In 16 total patients, they also found EBRT to have a tolerable side effect profile. There were no differences in >grade 2 toxicity between IBD and case control patients. As a caveat, it was found that acute ≥grade 2 toxicity differences were statistically higher in patients who underwent concurrent IBD medication and radiation therapy. Fifty-eight percent of men on concurrent therapy suffered ≥grade 2 toxicity while only 8% of non-medicated men had ≥grade 2 toxicity. There was no difference in toxicity detected for radiation technique IMRT vs. 3DCRT.

Murphy et al.[11] study presents several important points of contrast to our findings. Patients in our analysis suffered from somewhat higher rates of late ≥grade 2 GI toxicity at 17% versus 10% in the Murphy et al. study. With the small number of patients, it is uncertain whether the differences are significant, but it may be explained by 79% of the current patients being on concurrent IBD medication. Only 47% of the Murphy et al. cohort were on concurrent medication. This depicts that our patient cohort may have had more severe disease at baseline which required medical intervention. The difference in toxicity may also be attributed to our lack of exclusion for timing of patient's last IBD flares. Although Murphy et al. did not detect a difference between flare interval and radiation toxicity, they did exclude patients who suffered from a flare within a year of radiation. We did not exclude patients based on the timing of their last IBD flare, but we did exclude patients in an active flare. The final and likely the most notable reason for the difference resides in the coding of toxicity. In our analysis we used the National Cancer Institute designated CTCAE v4 common toxicity criteria, while Murphy et al. used an institutional designed scale. This makes a true comparison of toxicity between studies difficult.

A meaningful comparison for acute toxicity is hindered secondary to the limited available acute toxicity data on chart review, and thus we could not corroborate Murphy et al. findings concerning IBD medication use and increased acute toxicity. Regardless, with all of the above taken into consideration, irrespective of the differences between studies, radiation in non-flare IBD patients with prostate cancer appears to be a tolerable treatment option.

The current study suffers from the same constraints inherent in other retrospective reviews. The investigation is also limited by low patient numbers due to the disease subset being very rare. The sparsity of data is exemplified by our review of 160 records resulting in only 18 patients with the target combination of diagnoses and treatments over a 15-year period. Full dosimetric records were also not available for the majority of patients due to treatment delivery of more than 10 years ago. These record limitations provided for only minimal evaluation of dosimetric correlation to toxicity.

6. Conclusion

In the modern era of IMRT, this data offers some assurance that patients with IBD and prostate cancer can be administered radiation therapy without concern for significantly increased late GI toxicity.

Authors contributions

All authors contributed equally to the development and submission of the manuscript. Neither this manuscript in its entirety nor portions therein has been published previously nor is under consideration for publication elsewhere. All authors have approved the submission of this manuscript.

Conflict of interest

None declared.

Financial disclosure

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