Scientific Article

Toxicity After Stereotactic Body Radiation Therapy for Prostate Cancer in Patients With Inflammatory Bowel Disease: A Multi-institutional Matched Case-Control Series

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Received March 30, 2021; revised June 29, 2021; accepted July 7, 2021

Disclosure: Dr Collins reports grants and personal fees from Accuray Inc, personal fees from Boston Scientific, outside the submitted work. Dr Fuller reports grants, personal fees, and other from Accuray Inc, other from Varian Medical Systems Inc, and other from ViewRay Inc, outside the submitted work. Dr Aghdam reports grants from Accuray Inc, outside the submitted work. Dr Steinberg reports personal fees from ViewRay Inc, outside the submitted work. Dr Nickols reports grants from Bayer, grants from Gene Sciences Inc, grants from Janssen Pharmaceuticals Inc, grants from Prostate Cancer Foundation, grants from Varian Medical Systems, personal fees from Gene Sciences Inc, personal fees from Nanobiotix, personal fees from Progenics, other from Gene Sciences Inc, outside the submitted work. Dr Meier reports grants and personal fees from Accuray Inc, outside the submitted work. Dr Kishan reports personal fees from Varian Medical Systems Inc, personal fees from ViewRay Inc, and other from Janssen Pharmaceuticals Inc, outside the submitted work. Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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https://doi.org/10.1016/j.adro.2021.100759

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Abstract
Purpose: To evaluate the safety of stereotactic body radiation therapy (SBRT) for prostate cancer in men with inflammatory bowel disease (IBD).

Methods and Materials: We queried a consortium database for patients with IBD receiving SBRT for prostate cancer between 2006 and 2012. Identified patients were matched with patients without a history of IBD in a 3:1 fashion based on dose, fractionation, use of androgen deprivation therapy, and age distribution. Logistic regression was used to evaluate the association between having IBD and experiencing acute and late gastrointestinal (GI) and genitourinary (GU) toxicities as scored on the Common Terminology Criteria for Adverse Events scale. Time to late toxicity was evaluated using proportional hazard Cox models. Our study was limited by absence of data on prostate size, baseline International Prostate Symptom Score, and rectal dose-volume histogram parameters.

Results: Thirty-nine patients with flare-free IBD at time of treatment (median follow-up 83.9 months) and 117 matched controls (median follow-up 88.7 months) were identified. A diagnosis of IBD was associated with increased odds of developing any late grade GI toxicity (odds ratio [OR] 6.11, \( P < .001 \)) and GU toxicity (odds ratio 6.14, \( P < .001 \)), but not odds of developing late grade ≥2 GI (\( P = .08 \)) or GU toxicity (\( P = .069 \)). Acute GI and GU toxicity, both overall and for grade ≥2 toxicities, were more frequent in men with IBD (\( P < .05 \)). Time to late GI and GU toxicity of any grade was significantly shorter in patients with IBD (\( P < .001 \)). Time to late grade ≥2 GU, but not grade ≥2 GI toxicity, was also shorter in patients with IBD (\( P = .044 \) for GU and \( P = .144 \) for GI).

Conclusions: Patients with IBD who received SBRT for PCa had a higher likelihood of developing acute GI and GU toxicity, in addition to experiencing lower grade late toxicities that occurred earlier. However, patients with IBD did not have a higher likelihood for late grade ≥2 GI or GU toxicity after SBRT compared with the control cohort. Interpretation of this data are limited by the small sample size. Thus, men with IBD in remission should be properly counseled about these risks when considering SBRT.

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Introduction
Inflammatory bowel disease (IBD) is a clinical entity composed of Crohn disease and ulcerative colitis that is characterized by acute and chronic inflammatory states within the gastrointestinal (GI) tract. IBD may be associated with a slightly higher risk for developing prostate cancer (PCa), which is the most common noncutaneous malignancy among men in the United States. Most men with localized PCa warranting definitive treatment are treated with definitive external beam radiation therapy, radical prostatectomy, or brachytherapy. Historically, however, radiation therapy has been considered a relative, if not absolute, contraindication for patients with IBD. Thus, patients with IBD are often offered nonradiotherapeutic management.

Recent studies have challenged the notion that definitive radiation therapy for PCa leads to higher rates of late toxicity among patients with IBD. These case-control series have generally evaluated conventionally fractionated radiation therapy and included patients receiving brachytherapy to help identify sufficient cases for analysis. To our knowledge, no studies have been published evaluating any associations between a diagnosis of IBD and toxicity after stereotactic body radiation therapy (SBRT), which is an emerging standard of care option for PCa with a favorable efficacy and safety profile. In SBRT regimens, higher doses of radiation are delivered per fraction using sophisticated planning and delivery techniques. The delivery of significantly higher doses per day may affect toxicity considerations in patients with a history of IBD, although the precision necessitated by this approach may help minimize untoward increases in toxicity. The aim of this multicenter matched case-control study was to assess the GI and genitourinary (GU) toxicities after SBRT in PCa patients with and without IBD.

Methods and Materials
We queried a multi-institutional consortium of 2142 men treated with SBRT for PCa between 2000 and 2012 and identified patients with a documented history of IBD that was in remission (inactive IBD) at the time of treatment, as determined by the treating gastroenterologist. Inclusion criteria consisted of clinically localized PCa, treatment for PCa with SBRT, and documented history of IBD with either Crohn disease or ulcerative colitis, or IBD not otherwise specified. Men with active IBD at the time of SBRT were excluded from this retrospective analysis. All men received SBRT in 5 fractions with total dose being 35 Gy, 36.25 Gy, or 40 Gy. Details about this cohort have been previously published.

Next, we matched controls to the IBD cohort according to distribution of RT dose, fractionation, androgen deprivation therapy use, and age using a 3:1 matching process to identify controls. Common Terminology Criteria for Adverse Events, version 4 scoring criteria were used to grade GI and GU effects. The primary outcomes were acute and late grade ≥2 GI and GU toxicities. Crude incidences of toxicity among patients with IBD and matched controls were compared using Fisher exact test. Logistic regression was used to evaluate the association...
between IBD and GI or GU toxicity after SBRT. The association between IBD and time to late GI or GU toxicity was evaluated with Cox proportional hazard models. All tests for significance were 2-sided. A $P$ value less than .05 was considered statistically significant. All statistical analyses were carried out using SAS version 9.0 and R version 4.0.2.

**Results**

Baseline patient and treatment characteristics including dose-fractionation, androgen deprivation therapy use, and median follow-up for the IBD and control cohorts treated with SBRT are shown in Table 1. The IBD and control cohorts had median follow-up of 83.9 months (range, 66.8-94.9) and 88.7 months (range, 75.6-102), respectively. No patient in the IBD cohort had an active flare at the time of treatment. Crude incidences of acute and late toxicity are presented in Table 2 and Figure 1. The crude incidence of acute grade $\geq 2$ GI (7.7% vs 0%, $P = .015$) and GU (30.8% vs 3.4%, $P < .001$) toxicities were significantly higher in the IBD versus the control cohort. However, the IBD and control cohorts had no significant difference in crude incidences of late grade $\geq 2$ GI (5.1% vs 0%, $P = .061$) and GU (17.9% vs 7.7%, $P = .123$) toxicities. For patients with IBD, one patient experienced a late grade 2 GI toxicity event caused by diarrhea, and the majority of the late grade 2 GU toxicities included urinary frequency and retention. In the IBD cohort, there were no acute grade 3 GI or GU toxicity events. However, there were one late grade 3 GI (ana fistula requiring fistulotomy) and one late grade 3 GU (bladder tumor requiring fulguration) toxicity events, but no grade 4 events, in the IBD cohort.

Logistic regression models for acute and late toxicity are presented in Table 3. Compared with controls, patients with IBD had significantly higher odds of developing acute grade $\geq 2$ GI (odds ratio [OR] = 22.53; 95% confidence interval [CI], 1.12%-453.78%; $P = .042$) and acute grade $\geq 2$ GU toxicities (OR = 11.47; 95% CI 3.58%-36.70%; $P < .001$). However, IBD was not associated with higher odds of late grade $\geq 2$ GI ($P = .08$) or GU ($P = .069$) toxicities, although it was associated with time to late GI and GU toxicity.

Cox models for time to late GI and GU toxicity are shown in Table 4, and Kaplan-Meier curves of toxicity-free survival are shown in Figure 2. There was no significant difference in time to acute GI or GU toxicity between the IBD and control cohorts. However, the IBD cohort had significantly shorter time to late GI toxicity ($P = .001$) and GU toxicity ($P = .015$). In conclusion, patients with IBD had significantly higher odds of acute GI and GU toxicities after SBRT compared with controls. However, IBD was not associated with increased risk of late GI or GU toxicities, although it was associated with increased risk of time to late GI and GU toxicity.
significant difference in time to late grade ≥2 GI toxicity in patients with IBD (P = .14); however, patients with IBD had a significantly shorter time to late grade ≥2 GI toxicity (hazard ratio [HR] = 2.75; 95% CI, 1.03%-7.4%, P = .04). On Kaplan-Meier analysis, toxicity-free survival was significantly lower in patients with IBD with respect to both late grade ≥2 GI (P = .011) and GU (P = .039) toxicities.

**Discussion**

In this multi-institutional matched case-control cohort study we found that men with inactive IBD who received SBRT for PCa did not have significantly higher odds of late GI or GU grade ≥2 toxicity, although low-grade late GI and GU toxicities were significantly greater and time to toxicity was significantly shorter. Acute grade ≥2 toxicities were also significantly more common among patients with IBD. It must be acknowledged that the lack of a statistically significant increase in late toxicities in the IBD cohort may simply reflect the low sample size, and, as such, SBRT in this patient population must be approached with caution.

**Figure 1** Crude incidences of gastrointestinal (GI) and genitourinary (GU) toxicity among patients with inflammatory bowel disease and matched controls. Bar graph showing proportion of patients with acute or late GI or GU toxicity on the Common Terminology Criteria for Adverse Events v4.03 scale. Red, control; blue, patients with inflammatory bowel disease.

**Historically, IBD has been considered a contraindication to radiation therapy. In fact, the 2020 National Comprehensive Cancer Network guidelines suggest that inactive ulcerative colitis is a relative contraindication to treatment with radiation therapy, while active ulcerative colitis is an absolute contraindication.** The landmark PACE-B trial excluded patients with IBD from enrollment, as did many of the single-arm phase 2 studies included in consortium analyses that have reported on the overall safety of SBRT. However, several previous case-control reports have suggested that other forms of radiation, such as conventionally fractionated radiation therapy and brachytherapy, have a reasonable safety profile among patients with IBD.7,8

In contraindications to treatment, an international systematic review and meta-analysis, Lin et al reported incidence of radiation therapy-related acute and late toxicities among patients with collagen vascular disease and IBD. They found that patients with collagen vascular disease and IBD had a relatively low incidence of severe toxicity (10%-15% risk of any grade ≥3 toxicity, <5% risk of grade 4 toxicity, and <1% risk of grade 5 toxicity).14 Murphy et al compared with toxicity rates between 21 PCa patients with IBD and 63 matched controls (median follow-up of 49 months) who received external beam radiation therapy (either 3-dimensional conformal

**Table 3** Unadjusted logistic regression for development of toxicity in IBD cohort

|                  | OR (95% CI)    | P value |
|------------------|----------------|---------|
| GI Toxicity      |                |         |
| Any acute GI     | 4.13 (1.61-10.59) | .003    |
| Acute GI, grade ≥2 | 22.53 (1.12-453.78) | .042    |
| Any late GI      | 6.11 (2.1-17.77)  | <.001   |
| Late GI, grade ≥2 | 15.67 (0.72-339.57) | .080    |
| GU toxicity      |                |         |
| Any acute GU     | 6.49 (2.92-14.44)  | <.001   |
| Acute GU, grade ≥2 | 11.47 (3.58-36.70) | <.001   |
| Any late GU      | 6.14 (2.66-14.18)  | <.001   |
| Late GU, grade ≥2 | 2.64 (0.93-7.49)  | .069    |

Association of having IBD and experiencing GI and GU toxicities were evaluated using logistic regression.

**Abbreviations:** CI = confidence interval; GI = gastrointestinal; GU = genitourinary; IBD inflammatory bowel disease; OR = odds ratio.

**Table 4** Unadjusted proportional hazard Cox models for time to late toxicity in IBD cohort

|                  | HR (95% CI)    | P value |
|------------------|----------------|---------|
| GI Toxicity      |                |         |
| Any late GI      | 5.99 (2.18-16.46) | <.001   |
| Late GI, grade ≥2 | 15.99 (0.39-659.5) | .144    |
| GU Toxicity      |                |         |
| Any late GU      | 5.44 (2.69-11.01)  | <.001   |
| Late GU, grade ≥2 | 2.75 (1.03-7.4)   | .044    |

Time to late toxicity was evaluated using proportional hazard Cox models.

**Abbreviations:** CI = confidence interval; GI = gastrointestinal; GU = genitourinary; HR = hazard ratio; IBD inflammatory bowel disease.
radiation therapy or intensity modulated radiation therapy) or permanent interstitial low-dose-rate I-125 brachytherapy. They found that the IBD cohort had an increased incidence of acute grade $\geq 2$ GI toxicity and late grade $\geq 2$ GI toxicity, but these incidences were not significantly different from the control cohort. The authors reported one acute grade 3 GI and one late grade 3 GU toxicity event, but no grade 4 events. The results of our analysis comprising 39 men with IBD (median follow-up of 83.9 months) agree with the results from Murphy et al and Lin et al, and further support the notion that radiation therapy in patients with IBD may not be an absolute contraindication.

Extreme hypofractionation using SBRT for localized PCa is recognized as an appropriate treatment option with a favorable toxicity profile for men with localized PCa who do not have contraindications, such as IBD. Lehrer et al performed a meta-analysis of phase 3 randomized trials that characterized the efficacy and safety of ultrahypofractionated radiation therapy (SBRT) versus hypofractionated radiation therapy and conventionally fractionated radiation therapy among men with PCa without contraindications to therapy. They found that SBRT regimens appeared to offer similar levels of safety and efficacy compared with hypofractionated and conventionally fractionated regimens. The IBD cohort in our study developed lower incidence of late grade $\geq 2$ GI toxicity (5.1%) versus the conventionally fractionated arm (range, 5.4%-22%), hypofractionated arm (range, 8.9%-25.6%), and SBRT arm (10%). Furthermore, the IBD cohort in our study had a similar rate of late grade $\geq 2$ GU toxicity (17.9%) compared with the conventionally fractionated arm (range, 6.5%-45.6%), hypofractionated arm (range, 6.1%-49.3%), and SBRT arm (18%) in the Lehrer et al study. Together these results suggest that and SBRT in patients with IBD is not an absolute contraindication, use of SBRT should be approached cautiously as patients are at risk of developing late grade $\geq 2$ GU toxicity.

Our study is noteworthy because it shows that patients with IBD who were treated with SBRT had a toxicity profile (at a longer median follow-up than other studies) that is similar to that of patients with IBD who were treated with other forms of radiation therapy. However, the lack of individual patient data from those treated with more extended fractionation schemes or brachytherapy...
limits any conclusions that can be drawn, and further study is needed. Moreover, the increase in acute toxicity and potential for increased late toxicity, along with the clearly shorter toxicity-free survival, do raise concern for whether SBRT would be a preferred modality in this patient population, as most men likely have other treatment options. We found increased rates of acute ≥2 GI toxicity and lower rates of late grade ≥2 GI toxicity-free survival among patients with IBD, but otherwise no increased odds of late grade ≥2 GI toxicity or differences in time to late grade ≥2 GI toxicity. In comparison to the crude incidence data from Murphy et al, the IBD cohort in our study developed lower incidence of acute grade ≥2 GI toxicity (25% vs 7.7%) and late grade ≥2 GI toxicity (10% vs 5.1%). The IBD cohort had no acute grade 3 GI or GU toxicity events; but there were one late grade 3 GI and one late grade 3 GU toxicity events. Interestingly, we identified an increased rate of GU toxicity in both the acute and late settings, as well as a significantly shorter time to late grade ≥2 GU toxicity.

The greater likelihood of developing acute grade ≥2 GI and GU toxicities after SBRT in the IBD cohort may be associated to the underlying processes causing chronic inflammation in IBD patients and an immunomodulatory response from radiotherapy. Preclinical data suggests that SBRT-induced tumor cell death triggers the release of tumor antigens and inflammatory cytokines, which could increase the risk of developing both GI and GU toxicity. This is supported by the delayed occurrence of urinary symptoms after SBRT and rapid symptomatic response to oral steroids. On the other hand, the use of first line therapies for IBD, such as glucocorticoids, poses risk for development of comorbid conditions including cardiovascular and metabolic diseases. A study by Zaorsky et al found that men with unmanaged type 2 diabetes mellitus and men with type 2 diabetes mellitus receiving insulin had worse prostate cancer outcomes and toxicities than men without type 2 diabetes mellitus. Therefore, another possibility for the greater likelihood of developing acute grade ≥2 GI and GU toxicities after SBRT in the IBD cohort may be associated with underlying comorbidities. However, further research is needed to elucidate causes of post-SBRT toxicities.

There are several limitations to this study. It should be noted that while comparisons of toxicity data between the IBD cohort and controls did not reach significance, there was a trend to significance, and this could be an artifact of the small size of the cohort. There was unmeasured bias by treating physicians in recommending radiation therapy versus surgery, despite IBD and control cohorts having similar baseline characteristics. Data on prostate size, baseline International Prostate Symptom Score, and rectal dose-volume histogram parameters were not available for these patients. Furthermore, due to the retrospective design of this study, it was difficult to distinguish radiation colitis toxicity from the symptoms of IBD flareups. Lastly, details on immunomodulatory medications, flare-free interval before radiation, and comorbid conditions were not available in our data set.

Conclusions

This multicenter matched case-control study shows that compared with controls, SBRT-treated PCa patients with inactive IBD had a toxicity profile that is similar to previous reported studies analyzing toxicity of conventional fractionation. Although patients with IBD had a higher likelihood of developing acute grade ≥2 GI and GU toxicities, this difference was not seen in the long term follow-up (median follow-up of 83.9 months). However, interpretation of this data are limited by the small sample size. We do not recommend SBRT for patients who are in the midst of an active flare and caution treatment for those who had an acute flare in the year before SBRT. Moreover, given the potential for increased toxicity, caution should be taken when recommending SBRT to PCa patients with IBD who are in remission. Patients must be carefully counseled about the potential risks.

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