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Tolerability of Radiation Therapy in Patients with Inflammatory Bowel Disease

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Abstract

Conventionally, radiation therapy (RT) in patients with inflammatory bowel disease (IBD) patients is considered to cause serious gastrointestinal (GI) tract. Adverse events; thus, these patients are unable to receive the same RT as that administered to patients without IBD. However, it is unclear whether RT in IBD patients causes serious adverse events or poorly controlled IBD. The purpose of this study was to clarify the acute and late radiological GI toxicity in IBD patients.

Objective of the study: To evaluate the tolerability of radiation therapy in patients with inflammatory bowel disease.

Patients and methods: Data of IBD patients who received RT to the abdominal pelvis in our hospital between 1997 and 2017 were reviewed retrospectively. We excluded cases that were not irradiated to the GI tract. Radiation toxicity was examined according to the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). Toxicity that occurred within 90 days from the last administration of RT was defined as acute toxicity, while toxicity occurring thereafter was defined as late toxicity.

Results: Our study included 17 patients; nine with ulcerative colitis (UC), seven with Crohn's disease (CD), and one unknown case. The median follow-up period after irradiation was 19 months. Median total dose of RT was 50 Gy (range; 3-145). Median dose per fraction was 2 Gy (range; 1.8-8). 16 patients received three-dimensional external beam radiotherapy (3D-EBRT) and 1 patient received low dose rate (low dose rate) brachytherapy. Regarding irradiation field, the whole pelvis was used in two cases, small pelvis in two cases, tumour bed or local region in nine cases, total body irradiation (TBI) in three cases, and whole brain and total spinal cord in one case. No Grade 3 or higher GI toxicities were observed in either the acute or late phases. IBD activity exacerbations were not clearly observed after RT.

Conclusion: Our results indicated that RT of the abdomen or pelvis was tolerable in patients with IBD.

Keywords: Radiation; Inflammatory bowel disease; Acute toxicity; Late toxicity; Total body irradiation

Introduction

Inflammatory bowel disease (IBD) is a chronic idiopathic gastrointestinal (GI) disorder characterized by immunological inflammation with repeated exacerbation and remission. IBD includes ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC) [1,2]. IBD is a risk factor for colorectal cancer (CRC) and the morbidity rate increases with time [3]. Furthermore, the prognosis of CRC with IBD is poorer than that in patients without IBD [4,5]. However, the incidence of CRC has decreased due to the improvement of IBD activity by modern management methods, particularly surveillance by regular lower endoscopic examination; surgery; nutritional therapy; and the use of 5-aminosalicylate (5-ASA), steroids, immunosuppressant's, and anti-tumor necrosis factor alpha (TNFα) agents [4]. Although IBD occurs frequently in Europe and the United States, its incidence is increasing each year in Asian countries including Japan. The incidence rate of UC was reported to be comparable to those in Europe and the United States [6,7]. There were approximately 210,000 patients with IBD in Japan in 2013, the highest number among designated specific intractable diseases and about twice the number of patients reported in 2004 [6]. Around the beginning of the 21st century, several papers reported the potential for radiation therapy (RT) to the abdominal pelvis to cause severe acute and late GI toxicity in patients with IBD [8-10]. However, it was not clear if these toxicities were caused by adverse events due to RT or by the exacerbation of poorly controlled IBD. For this reason, there is no consensus on the safety of RT applied to the abdominal pelvis of patients with IBD. Therefore, the present study examined the frequencies of acute and late GI adverse events of RT in patients with IBD and assessed their impact on IBD activity.

Methods

Using the diagnostic disease name database in the medical information room, we identified and examined cases in which IBD patients received RT in our hospital between 1997 and 2017. We excluded cases in which the lower digestive tract was not irradiated. This was a retrospective study. IBD was defined as UC, CD, or IC. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). Late effects were defined as those emerging more than 90 days after completion of RT. This research was conducted with the approval of the ethics committee of the facility.

IBD activity was evaluated using the Mayo score for UC and International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) assessment score for CD [11,12]. To ensure objectivity, we calculated the IBD scores before and after RT using the Clinical Survey Personal Papers. We used the worst score after RT. Clinical Survey Personal papers are forms required by Japanese law ("Law concerning medical expenses for patients with designated intractable diseases", Law No. 50 of Heisei 26) for the delivery of Medical Beneficiary Certificate of the Medical Expenses Subsidy Program for Designated Intractable Disease Patients. The Clinical Survey Personal Papers are prepared once a year by a designated medical physician or cooperative designated physician. These forms are used to confirm that a patient is suffering from a designated intractable disease and presents with a certain level of symptoms. The designated physicians are required to have at least five years of experience with the diagnosis and treatment of the designated intractable diseases, have qualifications from related academic societies at the time of application, and have completed specific training. In addition, the license of these designated physicians must be renewed every five years. The cooperative designated physician is able to prepare the necessary medical certificates for a designated intractable disease at the time of renewal.

JMP Pro 13.1.0 was used for statistical analysis. IBD activity before and after radiation treatment was tested in two sides by T-tests of the Mayo and IOIBD assessment scores. $p<0.05$ was defined as a statistically significant difference.

Results

Seventeen patients with IBD who underwent RT of the abdomen or pelvis were enrolled in the present study. The patient, IBD, and tumor characteristics are shown in Table 1.

Gender (male/female)	**N (%)** **10(59)/7(41)**
Age diagnosed as IBD	19 (range; 0-65)
Age receiving RT	34 (range; 2-70)
IBD type	N (%)
UC	9(53)
CD	7(41)
Unknown	1(6)
Active IBD at baseline*	11(78)
History of IBD treatment	N (%)
5-ASA	10(58)
Surgery	9(53)
Steroid	4(23)
Anti-TNFα	4(23)
Immunosuppressant	0(0)
Primary neoplasm	N (%)
Rectal cancer	5(29)
Anal fistula cancer	2(12)
Anal canal cancer	1(6)
Prostate cancer	2(12)
Hepatocellular carcinoma	2(12)
Renal cell carcinoma	1(6)
DLBCL	1(6)
AML	1(6)
Blood cell phagocytosis synd	1(6)
Medulloblastoma	1(6)
Stage (TNM 7th)	N (%)
I-II	3(18)
III-IV	11(65)
Median observation month after RT	19 (range; 2-136)

Table 1: Characteristics of patients.

Nine cases had UC, seven had CD, and one case was unknown. The unknown case was excluded from the analysis of acute and late toxicities and IBD activity because it was the most severe type of Hoyeraal-Hreidarsson syndrome developed at birth. In the nearest Clinical Survey Personal Paper before RT was started, the activity of IBD were in 12 cases (70%). Eight cases (47%) were prescribed steroids and anti-TNF-α agents and nine cases (53%) received surgery for the treatment of IBD at the start of RT. The median observation period from the start of RT was 19 months (2 – 136 months). RT was performed for the following diseases: rectal cancer (five cases), anal fistula cancer (two cases), and anal canal cancer (one case). In addition, there were two cases of prostate cancer; two cases of hepatocellular carcinoma; and one case each of renal cell carcinoma, diffuse large B-cell lymphoma (DLBCL), acute myeloid leukemia (AML), blood cell phagocytosis syndrome (Hoyeraal Hreidarsson syndrome, the most severe type), and medulloblastoma, respectively. According to the TNM classification of malignant tumors, 7th edition, 11 cases (65%) were stage III-IV. All patients received regular follow-up by gastroenterologists.

All patients completed RT. The median dose was 50 Gy. The details of RT and concomitant therapy are shown in Table 2.

Radiation therapy	
Median Total dose	50 Gy (range; 3-145)
Median dose per fraction	2 Gy (range; 1.8-8)
Radiation method	N (%)
3D-EBRT	16(94)
LDR Brachytherapy	1(6)

Radiation field	N (%)
Tumor bed or local	9(53)
TBI	3(18)
Whole pelvis	2(12)
Small pelvis	2(12)
Whole brain and spinal cord	1(6)
Combination therapy	N (%)
Surgery	8(47)
Chemotherapy	5(29)
Bone marrow transplantation	3(18)
Endocrine therapy	1(6)

Table 2: The details of RT and concomitant therapy.

3D-EBRT, three-dimensional external beam radiotherapy; LDR: Low Dose Rate; TBI: Total Body Irradiation.

Three-dimensional external irradiation was performed in 16 cases and low dose rate brachytherapy was performed in one case. Regarding irradiation field, the whole pelvis was used in two cases, small pelvis in two cases, tumor bed or local region in nine cases, total body irradiation (TBI) in three cases, and whole brain and total spinal cord in one case. Among concomitant therapies, surgery was performed in eight cases, chemotherapy in five cases, bone marrow transplantation in three cases, and hormone therapy in one case.

The acute and late toxicities are described in Table 3.

	GI toxicity		**Other toxicity**	
	Acute	Late	Acute	Late
Grade 0 n (%)	12(70)	12(80)	8(47)	11(73)
Grade 1 n (%)	2(12)	3(20)	3(18)	1(7)
Grade 2 n (%)	3(18)	0(0)	4(24)	2(13)
Grade 3 n (%)	0(0)	0(0)	1(6)	1(7)
Grade 4 n (%)	0(0)	0(0)	1(6)	0(0)
Grade 5 n (%)	0(0)	0(0)	0(0)	0(0)
GI: Gastrointestinal.				

Table 3: Acute and late toxicity.

Among GI disorders, adverse events of Grade 3 or higher were not observed in either acute or late toxicities. Among other disorders, Grade 3 jaundice and Grade 4 elevated amylase (AMY) level were observed as acute toxicity in palliative irradiation administered to a patient with hepatic portal cholangiocarcinoma. These disorders were considered in the medical records to be due to the tumor itself. Grade 3 noninfectious cystitis was also observed as a late toxicity event in a 33-year-old woman with anal canal cancer who received 45 Gy irradiation to her whole pelvis and a 14.4 Gy boost to the tumor bed because of incomplete resection after surgery. The patient died from peritoneal dissemination and deep vein thrombosis one year after RT.

IBD activities before and after RT are shown in Figure 1.

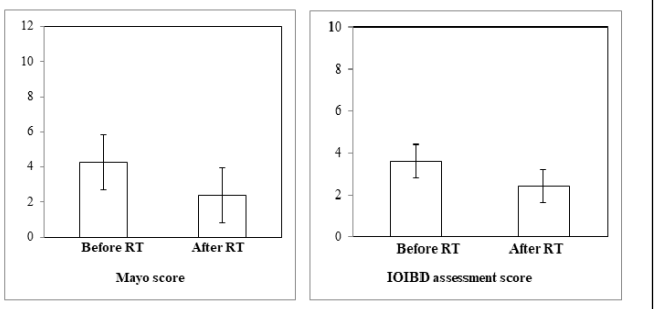

Figure 1: Statistically significant difference was observed.

There was no significant exacerbation in IBD activity before and after radiation treatment. The Mayo score for UC was t-value of -1.7, 6 degrees of freedom (dt), and a p-value of 0.13. The IOIBD score for CD had a t-value of -1.8, 6 dt, and p-value of 0.11.

Discussion

The biological mechanism of radiation toxicity is DNA damage of single and double-stranded fragments and hydroxyl radicals caused by ionizing radiation [13,14]. This induces cell cycle arrest, apoptosis, and necrosis due to DNA repair *via* p53 activation [15]. In comparison, GI toxicity due to radiation is more complicated. When intestinal epithelial stem cells present in the crypts of the intestinal epithelium are injured and depleted, the intestinal epithelium does not completely recover, resulting in the collapse of the barrier function and nutrient absorption of the epithelial structure and inflammation. Further tissue damage may be induced by various factors, including hydroxyl radicals produced by migrating leukocytes, fibrosis of normal tissue, and blood flow disturbance due to stenosis by internal thickening [16-18]. Although the mechanism of IBD has not been fully elucidated, it is widely accepted that inflammation in the intestinal tract is caused by abnormal mucosal immunity to intestinal flora and intestinal antigens [2]. As a result, inflammation due to mucosal damage by RT in IBD patients may be exacerbated by inappropriate activation due to exposure to the intestinal contents of the immune system. In addition, physiopathological studies have suggested an adverse effect of free radicals from IBD inflammation, deficiency DNA repair in IBD patients, and vasculitis and thrombosis related to IBD [19-22]. With these concerns, IBD patients who should receive RT in standard medical practice instead avoid RT and incur changes in the radiation field and total dose compared to those in non-IBD patients in clinical practice.

Since 2006, seven retrospective studies reported on acute and late toxicities after RT in more than 15 IBD patients. A prospective study also reported acute toxicity for high dose rate (HDR) brachytherapy in prostate cancer patients. These papers are detailed in Table 4.

Author	Bosch SL [23]	Mohammed W [24]	Chang BW [25]	Annede P [26]	White EC [27]	Murphy CT [28]	Peters CA [29]	Gestaut MM [30]
Study method	retrospective	prospective	retrospective	retrospective	retrospective	retrospective	Retrospective	Retrospective
No. patients	161	11	23	28	19	21	24	18
Period	1991-2010	2012-2015	1983-2011	1989-2015	1997-2011	1990-2011	1992-2004	1990-2013
Age	58 (range; 28-91)	N/S	60 (range; N/S)	N/S	64 (range; 35-84)	69 (range; 50-78)	N/S	67 (range; 58-78)
Female/male	57/104	0/11	7/16	11/17	4/15	0/21	0/24	0/18
IBD type UC CD IC	83 69 9	6 5	N/S	15 13	14 5	13 7 1	17 7	16 2
Active IBD at time of RT	N/S	1/11	N/S	5/28	1/19	1/21	0/24	N/S
Primary neoplasm	Rectal, sigmoid colon	Prostate	Cororectal, anal	12 prostate, 8 rectum, 5 cervix, 2 anal, 1 endometrial	8 prostate, 5 upper GI, 3 rectal/anal, 3 liver	Prostate	Prostate	Prostate
Radiotherapy method	3D-CRT, IMRT	HDR BT ± IMRT	3D-CRT, IMRT	2D-RT, 3D-CRT, IMRT, HDR BT, LDR BT	3D-CRT, IMRT	3D-CRT, IMRT, LDR BT	LDR BT ± 3D-CRT	3D-CRT, IMRT, LDR BT
Radiation dose (Gy)	SC-RT 25 LC-RT 45-50 CRT 45-50	HDR BT 15-20 ± IMRT 37.5	45-52	Various	54(range; 30-78)	EBRT 76(range; 10-80) LDR BT 145	LDR BT 124-160 LDR BT 100+EBRT 45	EBRT 70.2(range; 79.2-65) LDR BT 144(range; 100-144)
Concurrent chemotherapy	SC-RT none LC-RT none CRT 5-FU	None	CRC 5-FU Anal cancer 5-FU/MMC	Various	Various	None	None	None

Table 4: Summary of past reports.

N/S: Not Stated; UC: Ulcerative Colitis; CD: Crohn's Disease; IC: Indeterminate Colitis; 2D-RT: Two-Dimensional Radiotherapy; 3D-CRT: Three-Dimensional Conformal Radiotherapy; IMRT: Intensity-Modulated Radiation Therapy; HDR: High Dose Rate; LDR: Low Dose Rate; BT: Brachytherapy; SC-RT: Short Course Radiation; LC-RT: Long Course Radiation; CRT: Chemo-Radiation; 5-FU: 5-Fluorouracil; MMC: Mitomycin C; CRC: Colorectal Cancer.

Only one paper analyzed acute radiation toxicity in more than 50 patients. Bosch et al. compared acute toxicity after RT between no preoperative treatment and long-course radiation (LC-RT: 1.8-2 Gy × 25-28 fractions [fr]), short-course radiation (SC-RT: 5 Gy × 5 fr), and chemo-radiation (CRT; 5-FU added to LC-RT) in rectal cancer patients with IBD. The clinical target volumes included the perirectal and internal iliac and pre-sacral lymph node region. The rate of acute toxicities of grade 3 or higher was 0% (0/32) in SC-RT, 7.7% (1/13) in LC-RT, and 28.6% (6/21) in CRT. Severe acute toxicities were observed more often in the CRT group (p=0.004). However, there was no exacerbation of acute GI toxicity in IBD patients after RT. Two patients developed Grade 4 toxicities in the CRT group, including exacerbation of oral mucositis and bladder bleeding, respectively. The authors concluded that their results supported the use of standard preoperative RT for rectal cancer patients with IBD [23]. However, this report did not include OS and late toxicity data. Mohammed et al. reported the results of a prospective study of acute toxicity following HDR brachytherapy in prostate cancer patients with IBD. Nine patients received 19 or 20 Gy in one fraction with HDR brachytherapy. Two patients received 37.5 Gy IMRT followed by a 15 Gy HDR brachytherapy boost. Grade 3 or higher acute toxicities were not observed. The authors concluded that HDR brachytherapy was safe and well-tolerated in the short term by prostate cancer patients with IBD [24].

Regarding late toxicity, there is no safety consensus regarding abdominal pelvic RT for IBD patients. Chang et al. reported a tendency for IBD patients to experience severe late toxicity in the lower digestive tract compared to patients without IBD [25]. In contrast, Annede et al. reported that RT of the abdominal and pelvic region was acceptable [26]. However, that report was a retrospective study with a sample size of only 28 patients with varied characteristics of treatment, similar to that in the present study. Because the total dose and radiation field varied, it is possible that the safety of RT was overestimated. In some reports, late toxicity of the lower GI tract by IMRT or LDR brachytherapy for the abdominal and pelvic region was tolerable [27-30].

To our knowledge, only one report has considered the relationship between IBD activity and RT. Annede et al. reported exacerbation of IBD activity in 7.1% (2/17) of patients after RT. One case received 74 Gy (up to 46 Gy to the seminal vesicles) in external beam radiation therapy (EBRT), the other received 46 Gy in EBRT and 14 Gy in HDR brachytherapy for prostate cancer. Those two patients did not show IBD activity before RT. More than half of the patients maintained remission after RT [26]. In our study, no cases experienced exacerbation of IBD activity, as indicated by Mayo or IOIBD assessment score increases of 2 points or more; however, the average score tended to decrease. This might be due not only to three cases in which the IBD lesion sites in the intestinal tract were excised surgically but also to two cases in which the immune status changed following bone marrow transplantation, resulting in remission. In other cases, the scores were similar or increased by one. These results support the tolerability of RT in IBD patients. However, the IBD activity changed and the time of evaluation of Mayo and IOIBD assessment scores do not necessarily reflect the worst of clinical symptoms. Even with symptomatic exacerbation, symptoms may improve due to interventions by GI physicians and gastroenterologists; thus, we may have underestimated the IBD activity after RT. However, there was no uncontrollable exacerbation of IBD activity.

It is difficult for clinicians to objectively select IBD patients who can tolerate RT of the abdominal or pelvic regions. Annede et al. suggested a correlation between low BMI and high IBD activity [26]. In our study, all patients underwent routine follow-up by GI physicians and surgeons and received a lower GI endoscopy, colectomy, nutritional therapy, 5-ASA, steroids, immunosuppressants, and anti-TNFα agents. From this, we conclude that IBD activity can be managed in patients receiving RT to the abdominal or pelvic region in routine follow-up by GI physicians and surgeons.

Only one report has examined the prognosis after RT to the abdominal or pelvic region of CRC patients with and without IBD. Chang et al. reported no difference in overall survival between IBD and non-IBD patients who received RT [25]. This finding suggests that RT might have a role in improving prognosis, considering the poor prognosis for CRC in patients with IBD.

To our knowledge, Song et al reported the only case of total body irradiation (TBI) in an IBD patient, but details are unknown [8]. In our study, three cases received TBI as pre-treatment for hematopoietic stem cell therapy (HSCT). The first case was diagnosed with UC at 18 years of age, which recurred after remission induction therapy for AML at 23 years of age. She then received chemotherapy (daunorubicin/cytarabine) and TBI (4 Gy/2 fr) and cord blood transplantation (CBT) was done later. After that, she maintained a CR for 72 months, and the UC remained in remission with no late toxicity. The second case was diagnosed as CD at the age of 22 and recurred at 31 years of age after six courses of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) DLBCL. He then received chemotherapy (fludarabine/cyclophosphamide) and TBI (4 Gy/2 fr) and CBT was performed. After that, he maintained a CR for 36 months and his CD remained in remission with no late toxicity. The third case received CBT at 2 years of age for the most severe type of Hoyeraal-Hreidarsson syndrome, which was diagnosed at the age of 0 with blood cell phagocytosis syndrome and IBD complications. However, this case was transferred to another hospital and the details are unknown.

Qiu et al. reported clinical and endoscopic remission rates of 82.1% and 54.1%, respectively, for autologous hematopoietic stem cell transplantation (autologous HSCT) on intractable CD. Furthermore, even when IBD remission was not achieved, refractory IBD responded well to drug treatments that had no effect before autologous HSCT [31]. However, research on TBI and HSCT for IBD patients is scarce, and further reports and study are needed.

The pros of receiving radiation therapy for cancer patients with IBD may improve prognosis by receiving standard medical practice. Even if RT is not standard medical practice, RT becomes an option for cancer treatment in IBD patients. In our study, the cons were nothing.

The limitations of our research are its retrospective design, the small number of cases, and the variability in the radiation field and total doses administered. The dose of RT exposed to the GI tract volume correlates with GI acute and late toxicity. In our study, due to the low dose of RT to the GI tract, serious adverse events or exacerbation of IBD activity may not have been observed.

Conclusion

Our results indicated that RT of the abdomen or pelvis was tolerable in patients with IBD. However, further examination is needed regarding acute and late toxicities and IBD activity. In IBD patients, it may be necessary to consider using IMRT or brachytherapy to reduce the exposure dose to the GI tract.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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