

Radiation Exposure from Abdominal Imaging Studies in Patients with Intestinal Behçet Disease

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Background/Aims: Recently, several studies have revealed that diagnostic imaging can result in exposure to harmful levels of ionizing radiation in inflammatory bowel disease patients. However, the extent of radiation exposure in intestinal Behçet disease (BD) patients has not been documented. The aim of this study was to estimate the radiation exposure from abdominal imaging studies in intestinal BD patients. **Methods:** Patients with a diagnosis of intestinal BD established between January 1990 and March 2012 were investigated at a single tertiary academic medical center. The cumulative effective dose (CED) was calculated retrospectively from standard tables and by counting the number of abdominal imaging studies performed. High exposure was defined as CED >50 mSv. **Results:** In total, 270 patients were included in the study. The mean CED was 41.3 mSv, and 28.1% of patients were exposed to high levels of radiation. Computed tomography (CT) accounted for 81.7% of the total effective dose. In multivariate analyses, predictors of high radiation exposure were azathioprine/6-mercaptopurine use, surgery, and hospitalization. **Conclusions:** Approximately a quarter of intestinal BD patients were exposed to harmful levels of diagnostic radiation, mainly from CT examination. Clinicians should reduce the number of unnecessary CT examinations and consider low-dose CT profiles or alternative modalities such as magnetic resonance enterography. (**Gut Liver 2014;8:380-387**)

Key Words: Intestinal Behçet disease; Clinical course; Prognostic factors; Radiation

INTRODUCTION

The risks of protracted exposure to low-level ionizing radiation, including diagnostic radiation, have been acknowledged for decades, although the carcinogenic potential resulting from diagnostic radiation exposure has been debatable.¹ A study involving 15 developed countries reported that between 0.6% and 1.8% of all malignancies resulted from diagnostic medical radiation.² Irradiation with as little as 50 milli-Sieverts (mSv) from imaging-related radiation exposure has been implicated in the development of certain solid tumors, particularly of the large bowel and bladder.³

Inflammatory bowel disease (IBD) itself increases the risk of colorectal and small intestinal cancers⁴⁻⁶ and medications such as azathioprine, 6-mercaptopurine (6-MP), and infliximab are associated with an increased risk of lymphoma.^{7,8} This is of clinical concern for IBD patients, as IBD often presents at a young age and patients are thus repeatedly exposed to diagnostic medical radiation over the course of their disease, further increasing the risk of malignancy. Several recent studies examined radiation exposure from diagnostic medical imaging in IBD patients and reported that 5% to 24% of IBD patients have received potentially harmful levels of radiation, defined as ≥ 50 mSv.⁹⁻¹⁴

Intestinal Behçet disease (BD) is diagnosed by the presence of typical intestinal ulcers and systemic symptoms meeting the BD diagnostic criteria.¹⁵ Similarly to IBD, including Crohn's disease (CD) and ulcerative colitis, intestinal BD is a chronic IBD having a fluctuating course characterized by repeated episodes of relapse and remission.¹⁶ The chronic relapsing nature of intestinal BD often requires repeat diagnostic imaging. In addition, diagnostic imaging is essential for patients with in-

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testinal BD for perioperative evaluation because intestinal BD often requires surgical treatment due to the high frequency of complications, such as intestinal perforations and fistulas.¹⁷⁻¹⁹ Radiation exposure from diagnostic imaging is expected to become increasingly common for intestinal BD patients as it has for IBD patients, especially with increasing access to computed tomography (CT). However, the extent of diagnostic radiation exposure in patients with intestinal BD has never been specifically studied. Moreover, it would be valuable if patients at risk for a high level of radiation exposure could be identified, as this might help in minimizing the risk in these patients. Accordingly, the objective of this study was to examine the cumulative effective ionizing radiation exposure from all abdominal imaging studies in a large number of patients with intestinal BD. In addition, we sought to identify factors associated with exposure to high levels of diagnostic radiation.

MATERIALS AND METHODS

1. Study population and clinical evaluation

All patients with an established diagnosis of intestinal BD who were registered in the intestinal BD database at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, between January 1990 and March 2012, were eligible for inclusion in the study. Patients who were at least 18 years old at diagnosis and who had been followed up for at least 6 months were included. Baseline clinical, endoscopic, and laboratory characteristics were extracted from a prospectively-collected database. Information regarding hospitalization, operation, and medical treatment modalities during the follow-up periods was obtained by reviewing medical records.

Intestinal BD was diagnosed according to established criteria based on colonoscopic features and clinical manifestations.¹⁵ Patients classified as definite, probable, and suspected were included in the study.

Some patients were first diagnosed with intestinal BD during surgery performed due to an acute or complicated presentation such as perforation. All other patients underwent colonoscopy at the time of diagnosis to identify the location and shape of the intestinal ulcer. Lesions with less than five ulcers that were oval in shape, deep, had discrete borders, and were located in the ileocecal area were defined as typical ulcerations.²⁰ Ulcerations that did not fulfill all of these criteria were defined as atypical. Surgery was defined as an intestinal resection related to intestinal BD. The definition of hospitalization included only intestinal BD-related admissions.

Intestinal BD activity was measured using the disease activity index for intestinal Behçet disease (DAIBD), as described.²¹ The DAIBD ranges in value from 0 to 325, with higher scores reflecting greater disease activity.

Table 1. Radiation Dose from Common Abdominal Imaging Studies

Imaging study	Effective dose of radiation, mSv
Plain abdominal X-ray	0.7
CT abdomen	10
CT pelvis	10
Small bowel follow-through	3
Barium enema	7.2

CT, computed tomography.

2. Determination of radiation exposure

Almost all imaging resulting in exposure to diagnostic medical radiation consisted of plain abdominal X-rays (AXR), CT scans of the abdomen and/or pelvis, CT enterography (CTE), small bowel follow-through (SBFT), and barium enema. The total effective dose of radiation received from AXR, SBFT, and barium enema was each calculated according to published standardized tables (Table 1).²² The effective dose for CT of the abdomen and/or pelvis and CTE were calculated by multiplying the dose-length product (DLP) by a factor of 0.015, which is the dose conversion factor for the abdomen and pelvis according to the guidelines provided in Publication 103 of the International Commission on Radiological Protection.²³ When the DLP of CT of the abdomen and/or pelvis was not recorded in CT scan reports it was estimated based upon published standardized tables (Table 1). Cumulative effective dose (CED) was calculated for each patient by summing the effective doses of radiation from the time of diagnosis of intestinal BD until the time of data review. High cumulative exposure to diagnostic radiation was defined as CED exceeding 50 mSv.

This study was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea.

3. Statistical analysis

The software program SPSS version 12 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The chi-square or Fisher exact test was used to compare categorical variables. Student t-test or the Mann-Whitney U test was used to compare numerical variables between groups. p-values <0.05 were considered statistically significant. We constructed multivariate logistic regression models to identify independent factors associated with high CED (≥ 50 mSv). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

RESULTS

1. Patient demographics

A total of 270 patients with intestinal BD were included. Their mean age at diagnosis of BD, the onset of intestinal symptoms, and the diagnosis of intestinal BD were 38.7, 40.6, and 41.4 years, respectively. Of 270 patients, 123 (45.6%) were men

and the mean follow-up duration after diagnosis was 7.5 years (range, 0.5 to 22.3 years). The most common intestinal symptom and location were abdominal pain (217 patients, 80.4%) and ileocecal area (255 patients, 94.4%), respectively. Twenty-eight patients who were first diagnosed at the time of operation as having intestinal BD were excluded from the analysis of colonoscopy characteristics.

2. Diagnostic radiation exposure

The total number of abdominal imaging examinations among all patients was 3,114, of which 2,623 (84.2%), 433 (13.9%), 50 (1.6%), and eight (0.3%) were AXR, CT (of these, 40 [1.3%] were CTE), SBFT, and barium enema, respectively. CT imaging accounted for 81.7% (9,103/11,146 mSv) of total effective dose from abdominal imaging studies (Fig. 1). The mean and median CED per patients from abdominal imaging were 41.3 and 15.8 mSv, respectively. The annual mean and median effective dose were 11.1 and 1.4 mSv/yr, respectively. One hundred and sixty-eight patients (62.2% of cohort) underwent at least one abdominal imaging study. Seventy-six of the 270 patients (28.1%) received CED exceeding 50 mSv (Fig. 2).

3. Factors associated with high cumulative exposure to diagnostic radiation

Table 2 shows the differences between patients with a CED greater and less than 50 mSv. The mean age at diagnosis of intestinal BD, age at onset of intestinal symptoms, and age at diagnosis of BD were all significantly lower in patients with a CED \geq 50 mSv than those with a CED <50 mSv. White blood cell count, erythrocyte sedimentation rate, C-reactive protein level, and DAIBD at diagnosis were significantly higher in patients with a CED \geq 50 mSv than those with a CED <50 mSv, whereas albumin levels were significantly lower in patients with a CED \geq 50 mSv than those with a CED <50 mSv. Volcano-shaped

ulcers were more common in patients with a CED \geq 50 mSv, while oval and geographic-shaped ulcers were more common in patients with a CED <50 mSv. During the follow-up period, intestinal perforation and fistula occurred more frequently in patients with a CED \geq 50 mSv than in those with a CED <50 mSv. In addition, patients with a CED \geq 50 mSv required more frequent corticosteroid therapy, azathiopurine (AZA)/6-MP therapy, surgical treatment, and hospitalization than those with a CED <50 mSv.

No statistical differences in terms of sex, disease duration, family history of BD, symptoms and signs of systemic BD, type of intestinal ulcer, or diagnostic subtype were observed between patients with a CED greater and less than 50 mSv. In a multivariate logistic regression analysis that included significant variables from the univariate analysis, AZA/6-MP use (OR, 2.60; 95% CI, 1.10 to 6.16; $p=0.030$), surgery (OR, 3.35; 95% CI, 1.20 to 9.39; $p=0.022$), and hospitalization (OR, 4.11; 95% CI, 1.32 to 12.82; $p=0.015$) were independent explanatory factors associated with a high CED (Table 3).

DISCUSSION

Although several studies have reported significant diagnostic radiation exposure among patients with IBD, this study is the first to investigate the cumulative effective ionizing radiation exposure of patients with intestinal BD and to identify the subgroups of patients who are at greater risk of high cumulative exposure.

We found that a substantial proportion of intestinal BD patients were exposed to high doses of ionizing radiation from diagnostic tests. Over a mean follow-up period of 7.5 years, approximately a quarter of intestinal BD patients (28.1%) received cumulative doses in excess of 50 mSv, and the mean CED for intestinal BD was 41.3 mSv. Several recent studies investigat-

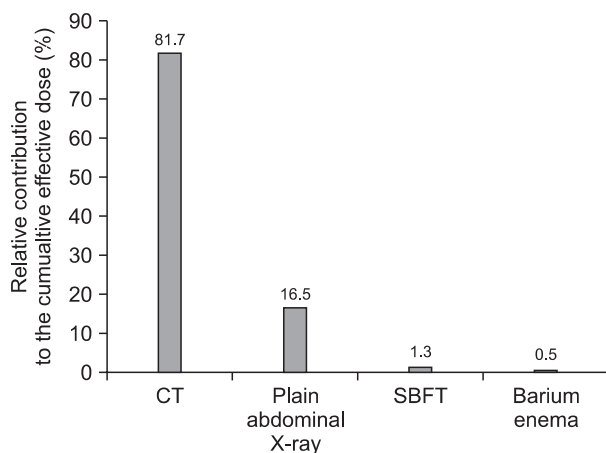


Fig. 1. Relative contribution of abdominal imaging studies to the cumulative effective dose in patients with intestinal Behçet disease. CT, computed tomography; SBFT, small bowel follow-through.

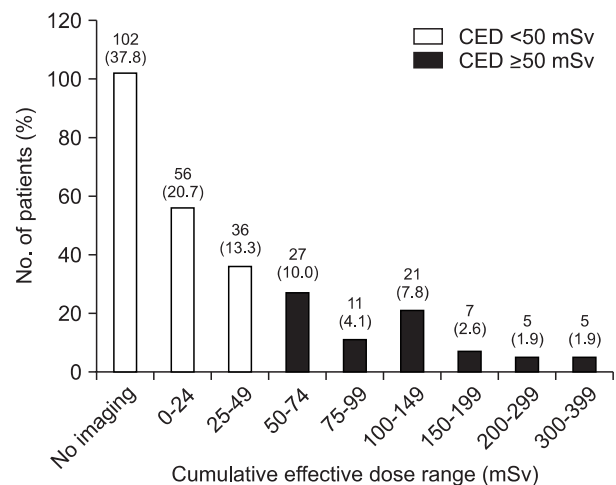


Fig. 2. Cumulative effective dose (CED) of abdominal imaging studies in patients with intestinal Behçet disease.

Table 2. Univariate Analysis of Factors Associated with Cumulative Effective Dose ≥ 50 mSv

Factor	CED <50 mSv (n=194)	CED ≥ 50 mSv (n=76)	p-value
Age at diagnosis of intestinal BD, yr	42.5 \pm 12.1	38.6 \pm 11.1	0.015
Age at onset of intestinal symptoms, yr	41.7 \pm 12.4	37.7 \pm 11.3	0.014
Age at diagnosis of BD, yr	39.8 \pm 12.5	35.9 \pm 11.0	0.018
Male sex	91 (46.9)	32 (42.1)	0.476
Disease duration, yr	7.4 \pm 5.1	7.8 \pm 4.6	0.511
Family history of BD	8 (4.1)	1 (1.3)	0.452
Symptoms and signs of BD			
Oral ulcer	175 (90.2)	74 (97.4)	0.073
Genital ulcer	76 (39.2)	39 (51.3)	0.070
Ocular lesion	35 (18.0)	16 (21.1)	0.570
Skin lesions	81 (41.8)	36 (47.4)	0.402
Arthritis/arthralgia	60 (30.9)	25 (32.9)	0.754
Laboratory findings at diagnosis			
WBC, 10 ⁶ /L	7,979 \pm 3,500	9,977 \pm 5,316	0.003
Hemoglobin, g/dL	12.1 \pm 2.0	11.9 \pm 2.4	0.578
ESR, mm/hr	32.5 \pm 25.9	42.7 \pm 31.3	0.013
CRP, mg/dL	1.7 \pm 2.4	4.4 \pm 4.9	<0.001
Albumin, g/dL	4.2 \pm 0.6	3.9 \pm 0.7	0.002
DAIBD* at diagnosis	61 \pm 40	95 \pm 47	<0.001
Shape of intestinal ulcer*			
Oval/geographic	129 (73.7)	35 (52.2)	0.001
Volcano	46 (26.3)	32 (47.8)	
Types of intestinal ulcer*			
Typical type	104 (59.4)	40 (59.7)	0.969
Atypical type	71 (40.6)	27 (40.3)	
Diagnostic subtypes of intestinal BD*			
Definite	79 (45.1)	34 (50.7)	0.137
Probable	73 (41.7)	30 (44.8)	
Suspected	23 (13.1)	3 (4.5)	
Intestinal complication			
Perforation	14 (7.2)	19 (25.0)	<0.001
Fistula [†]	7 (3.6)	13 (17.1)	<0.001
Stricture	12 (6.2)	6 (7.9)	0.613
Abscess	5 (2.6)	3 (3.9)	0.691
Medication			
5-ASA/sulfasalazine	179 (92.3)	72 (94.7)	0.476
Corticosteroids	70 (36.1)	65 (85.5)	<0.001
Azathiopurine/6-MP	38 (19.6)	48 (63.2)	<0.001
Surgery [*]	40 (20.6)	45 (59.2)	<0.001
Hospitalization [§]	89 (45.9)	70 (92.1)	<0.001

Data are presented as mean \pm SD or number (%).

CED, cumulative effective dose; BD, Behçet disease; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAIBD, disease activity index for intestinal Behçet disease; 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine.

*Twenty-eight patients who were first diagnosed with intestinal BD at the time of operation were excluded from the analysis of colonoscopic characteristics; [†]Excluded anal fistula formation; [‡]Intestinal resection related to intestinal BD; [§]Intestinal BD-related admission.

Table 3. Multivariate Analysis for Factors Associated with Cumulative Effective Dose ≥ 50 mSv

Factor	OR	95% CI	p-value
Age at diagnosis of intestinal BD, yr*	0.95	0.81-1.11	0.495
Age at onset of intestinal symptoms, yr*	1.00	0.88-1.14	0.987
Age at diagnosis of BD, yr*	1.04	0.95-1.14	0.404
Laboratory findings at diagnosis			
WBC, $10^6/L$	1.00	1.00-1.00	0.141
ESR, mm/hr	1.00	0.99-1.02	0.765
CRP, mg/dL	1.10	0.96-1.27	0.158
Albumin, g/dL	1.52	0.71-3.22	0.280
DAIBD* at diagnosis	0.99	0.98-1.01	0.499
Shape of intestinal ulcer (volcano vs oval/geographic)	0.70	0.30-1.63	0.405
Perforation	2.90	0.65-12.92	0.162
Fistula [†]	1.27	0.31-5.27	0.738
Corticosteroids	2.83	0.96-8.32	0.059
Azathiopurine/6-MP	2.60	1.10-6.16	0.030
Surgery [‡]	3.35	1.20-9.39	0.022
Hospitalization [§]	4.11	1.32-12.82	0.015

OR, odds ratio; CI, confidence interval; BD, Behçet disease; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAIBD, disease activity index for intestinal Behçet disease; 6-MP, 6-mercaptopurine.

*Mean \pm SD; [†]Excluded anal fistula formation; [‡]Intestinal resection related to intestinal BD; [§]Intestinal BD-related admissions.

ing radiation exposure from diagnostic medical imaging in CD patients have reported that the mean CED for CD patients was 14.3 to 36.1 mSv^{10-14,24} and the proportion of CD patients having an estimated CED ≥ 50 mSv was 7.0% to 23.7%.^{9,10,12-14} Our results showed that Korean intestinal BD patients were exposed to higher levels of ionizing radiation from diagnostic studies than Western CD patients, although they were indirectly compared. Because intestinal BD is rare, clinicians may have less experience with it and may thus order unnecessary radiologic examinations. Our results suggest that Korean clinicians caring for intestinal BD patients need to be cautious of ordering unnecessary radiologic examinations. In addition, clinicians need to consider cumulative radiation exposure and perform radiologic examinations only when the results can affect the patient's management.

Our recent study found that there were no significant differences in the long-term clinical outcomes between CD and intestinal BD and that CD patients required corticosteroid or immunosuppressant therapy more often than intestinal BD patients.²⁵ Therefore, Korean intestinal BD patients may not be exposed to higher levels of diagnostic radiation than Korean CD patients. Actually, a very recent study of Korean CD patients reported that the mean CED was 53.6 mSv, and 34.7% of patients were exposed to high levels of radiation (CED >50 mSv).²⁶

This study showed that approximately 80% of radiation ex-

posure in intestinal BD patients was from abdominal CT. Most studies on radiation exposure of IBD patients have also found that CT contributed the majority of the total effective dose administered to IBD patients.^{10-13,24} Our recent study showed that intestinal complications such as intestinal fistulas, stricture, and abscesses were less frequent in intestinal BD than in CD and that small bowel involvement was uncommon in intestinal BD.²⁵ Moreover, most patients with intestinal BD have localized colon involvement with ileocecal concentration and thus colonoscopy may be sufficient to diagnose intestinal BD and identify disease extent. This suggests that the demand for CT examinations may be less in intestinal BD than in CD. However, contrary to our expectation, patients with intestinal BD were exposed to high levels of radiation owing to CT examination. The effective dose of radiation from CT is high compared to other modalities.²² Therefore, reducing the number of unnecessary CT examinations is critical to minimizing diagnostic medical radiation. It has been estimated that, in the United States, up to one-third of all CT scans are done when alternative modalities could be used with equal efficacy or are repeated unnecessarily.²⁷ Recent advances in CT technology allow for significant reductions in radiation dose compared with current techniques.²⁸ Several studies have shown that radiation dose can be reduced 30% to 50% without sacrificing the diagnostic performance of CTE in CD patients.²⁹⁻³¹ We suggest that low-dose CT profiles should be made available for intestinal BD patients at risk for high radiation exposure. Magnetic resonance (MR) enterography has recently emerged as a promising diagnostic tool in assessment of patients with CD. Several studies have reported that MR is not inferior to CT in diagnosing CD or assessing bowel damage in CD.^{32,33} MR enterography should be considered as an alternative diagnostic tool in assessment of patients with intestinal BD, although no data are available regarding the usefulness of MR enterography in intestinal BD. Further studies are warranted to confirm the availability of MR enterography in intestinal BD.

In this study, AZA/6-MP use, intestinal BD-related surgery, and hospitalization were independent predictors of increased radiation exposure for intestinal BD. Patients with clinical markers of increased disease severity such as requirement for immunosuppressants, surgery, or hospitalization underwent more diagnostic imaging modalities to guide further management. AZA and 6-MP have been associated with an increased risk of lymphoma in IBD patients.⁷ Although lymphoma risk in intestinal BD patients treated with these medications has never been examined, AZA/6-MP use and radiation exposure by diagnostic imaging could synergistically increase the development of malignancies. Intestinal BD often requires surgical treatment because of the high frequency of acute complications such as intestinal perforations.^{19,34} Intestinal BD also recurs frequently, even after surgical treatment, and occasionally requires repeated surgery.^{19,34} The reason surgery was associated with increased radiation exposure could be because of repeated assessments

before deciding on surgery and the need to monitor postoperative complications. Recent studies in Western countries showed similar results concerning risk factors for increased radiation exposure in IBD patients. Palmer *et al.*³⁵ showed that hospitalization and surgery were associated with high cumulative exposure in IBD. Several other studies and a meta-analysis of six studies also revealed that surgery is a predictor of excessive radiation exposure in IBD patients.^{10-13,36}

To date, about 10 studies examined the diagnostic radiation exposure of IBD patients. However, only one of these studies investigated the incidence of cancer. Desmond *et al.*¹⁰ study which included 354 CD patients reported that during the follow-up period (mean, 6.7 years), malignancies occurred in seven patients, five of whom developed skin cancers and two of whom were diagnosed with gastrointestinal (GI) malignancy. In all but one case, CED was less than 75 mSv when the cancer was diagnosed. Therefore, a causal link with diagnostic radiation exposure is not clear. Of 270 intestinal BD patients who included in this study, no one developed malignancy. Although there is no evidence that intestinal BD is associated with GI malignancies to date and there is no data available regarding radiation risk for cancer in intestinal BD or IBD, several studies provide information regarding risk of radiation-induced cancer. It is estimated that up to 2% of malignancies could be attributed to diagnostic medical radiation and there are 5,500 deaths due to radiation-induced cancer in the United States each year.^{2,37} In addition, the U.S. National Research Council estimates that one patient will develop a radiation-induced cancer in their lifetime out of every 1,000 patients undergoing a 10 mSv CT abdominal scan.³⁸ Although these estimations were from general population, we expect the similar results from patients with intestinal BD or IBD. Considering the low overall incidence of cancers in patients with IBD and the low incidence of intestinal BD, large cohort study with follow-up extended to several decades is needed to acquire information regarding radiation risk for cancer in IBD or intestinal BD.

Our study had several limitations. First, this study did not include non-GI imaging in calculating exposure, which could result in underestimation of the total effective dose of radiation received. However, most non-GI imaging would have been plain radiographs, and radiation exposure from these investigations is negligible compared to CT. The effective dose from a chest X-ray (CXR), for example, is around 0.02 mSv, and the effective dose from CT scan of the abdomen and pelvis is equivalent to the effective dose of approximately 1,000 CXRs. Second, this was a retrospective study with a potentially biased design. However, the retrospective nature of the study could be construed as an advantage. The retrospective approach could avoid any confounding influence on investigator behavior that may occur with a prospective study and more accurately reflect clinical practice. Third, the estimated radiation dose, based on published standardized tables, may have been greater or less than the

actual exposure. However, we captured the DLP for approximately two-thirds of the CT scans performed and the calculated mean values (20.6 mSv) were similar to standard estimates of CT scans of the abdomen and pelvis (20 mSv). Finally, this was a hospital-based study and thus referral-center bias with inclusion of more severe cases in our cohort cannot be excluded, although patients with intestinal BD are generally managed by gastroenterology specialists in Korea.

In conclusion, the exposure to diagnostic radiation in patients with intestinal BD was high, mainly due to CT examination. One in four patients with intestinal BD was exposed to harmful amounts of diagnostic radiation. Patients who required immunosuppressants such as AZA/6-MP, surgery, or hospitalization were at greater risk of high radiation exposure. Given that intestinal BD is a life-long illness, clinicians caring for patients with intestinal BD need to consider cumulative radiation exposure, particularly from repeated CT scanning, and should perform these examinations only when the results can affect the patient's management. In addition, the availability of low-dose CT profiles and alternative imaging modalities such as MR imaging needs to be increased.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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