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Frequency and Risk Factors of Advanced Neoplasia in Korean Inflammatory Bowel Disease Patients with Low-grade Dysplasia

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Background/Aims: Studies on the clinical outcomes after detecting low-grade dysplasia (LGD) in patients with inflammatory bowel disease (IBD) are insufficient. This study evaluated the clinical features, frequency, and risk factors for advanced neoplasia in patients with IBD after an LGD diagnosis.

Methods: The medical records of 166 patients with IBD from six university hospitals in Korea from 2010 to 2019 were reviewed retrospectively. LGD was diagnosed in all patients during surveillance. The frequency and risk factors for advanced neoplasia were evaluated, and the clinical features of patients with and without advanced neoplasia were compared.

Results: Advanced neoplasia developed in 12 patients (six with large LGD, three with tubulovillous adenoma, and three with high-grade dysplasia), and all cases developed from UC. Patients with advanced neoplasia had significantly higher Mayo scores, and colitis-associated dysplasia was more common than sporadic lesions (83.3% vs. 29.9%; $p < 0.001$). Multivariate analysis showed that colitis-associated LGD significantly increased the risk of developing advanced neoplasia (odds ratio [OR], 10.516; 95% confidence interval [CI], 2.064–53.577). Among patients with colitis-associated lesions, a significant risk factor for advanced neoplasia was a prior history of LGD (OR, 9.429; 95% CI, 1.330–66.863).

Conclusions: Advanced neoplasia developed in 7.2% of patients with IBD and LGD. Most advanced neoplasms developed from colitis-associated lesions, and the risk was higher in patients with a history of LGD before index colonoscopy. (Korean J Gastroenterol 2025;85:34-43)

Key Words: Colorectal neoplasm; Inflammatory bowel disease; Risk factors

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INTRODUCTION

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory gastrointestinal (GI) disorders¹ that carry a significant risk of colorectal cancer (CRC).^{2,3} Patients with IBD have a 1.7-fold higher risk of CRC because of long-standing chronic inflammation and the possible occurrence of colitis-associated and sporadic neoplasia.² Therefore, most guidelines recommend surveillance colonoscopy to reduce the risk of dysplasia and CRC.⁴⁻⁷ In particular, the ECCO guidelines recommend surveillance colonoscopy based on the patient's risk.⁴ Nevertheless, interval cancer may still occur in patients with IBD if the lesions are missed during surveillance, and one study reported that it occurred in up to 30% of patients.⁸

In IBD patients, colitis-associated CRC (CA-CRC) progresses from chronic inflammation to CRC through dysplastic precursor lesions such as indefinite, low-grade, and high-grade dysplasia.⁹ A follow-up cohort study after diagnosing low-grade dysplasia (LGD) in IBD patients reported a 21.7% incidence of advanced colorectal neoplasia (ACRN) after 15 years.¹⁰ On the other hand, the frequency of progression to high-grade dysplasia (HGD) or CRC varied from 16 to 54%.¹¹ Indefinite dysplasia (IND) was diagnosed when regeneration and dysplasia could not be distinguished clearly in an environment such as severe active inflammation.¹² The risk of ACRN was reported to increase in those with IND. Moreover, LGD was associated with a sig-

nificantly higher risk of ACRN compared with IND.¹³

Regarding management, endoscopic resection and regular close follow-up could also be considered in visible colitis-associated dysplasia with clear margins. Nevertheless, limited data exist for LGD/IND in patients with IBD regarding endoscopic treatment (endoscopic resection or surgery), follow-up interval, clinical course, or associated risks. Therefore, this study conducted a multicenter analysis of the clinical features, treatment, follow-up period, incidence of advanced adenoma, and risk factors for LGD/IND in Korean patients with IBD.

SUBJECTS AND METHODS

1. Patients

This study retrospectively reviewed patients with IBD who had been diagnosed with low-grade/indefinite dysplasia on surveillance colonoscopy and underwent at least one surveillance colonoscopy after detection at one of six university hospitals in Korea. The diagnoses of UC and CD were based on clinical, endoscopic, histopathological, and radiology findings.^{14,15} The baseline characteristics of the patients were obtained from the electronic medical data of each hospital, including the patient's demographics, type and disease status of IBD, comorbid diseases, accompanying primary sclerosing cholangitis (PSC), family history of CRC, smoking status, and medication records at the time of diagnosis of colon dysplasia

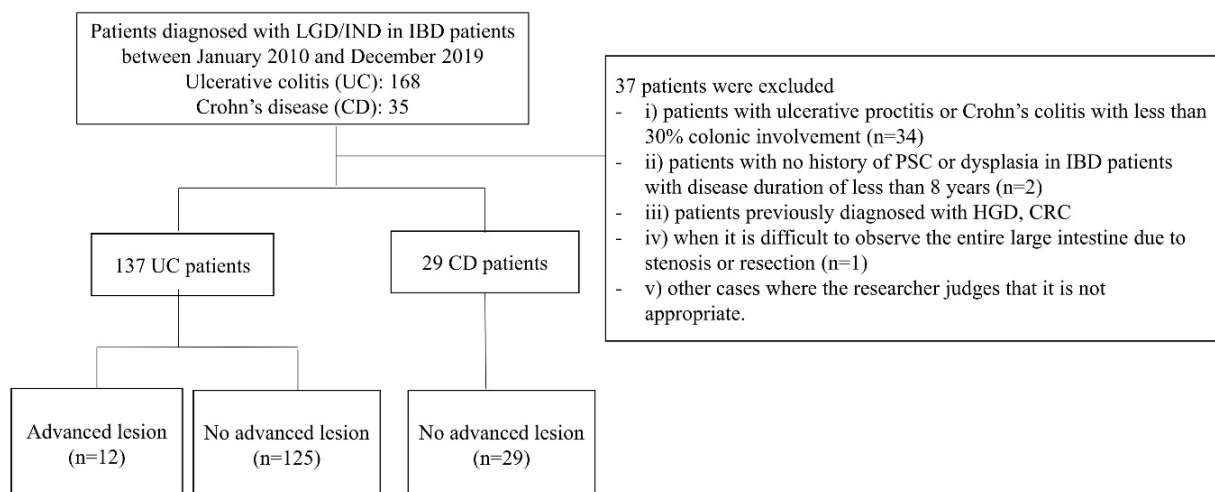


Fig. 1. Flow diagram of patient selection. LGD, low grade dysplasia; IND, indefinite dysplasia; IBD, Inflammatory bowel disease; PSC, primary sclerosing cholangitis; HGD, high grade dysplasia; CRC, colorectal cancer.

(<3 months).

The inclusion criteria were IBD patients with low-grade/indefinite dysplasia between 2010 and December 2019, who had undergone at least one surveillance colonoscopy, and who satisfied any of the following conditions: i) disease duration of eight years or more, ii) patients with PSC regardless of disease duration, iii) patients with a history of diagnosis of LGD, or iv) family history of CRC in first-degree relatives under the age of 50.

Thirty-seven patients were excluded based on the following exclusion criteria: i) patients with ulcerative proctitis or Crohn's colitis with less than 30% colonic involvement, ii) no history of PSC or dysplasia in IBD patients with disease duration of less than eight years, iii) patients previously diagnosed with HGD and CRC, iv) difficulty observing the entire large intestine due to stenosis or resection, and v) other cases where the researcher judged that it was inappropriate. Thus, 166 patients were included in the final analysis. The patients were divided into groups with and without advanced lesions, and the disease status of IBD, polyp type, treatment methods, and risk factors were investigated (Fig. 1). This study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the Institutional Review Board of each hospital.

2. Assessment of IBD

The disease extent and severity were classified using the Montreal classification in patients with UC, and the Vienna Montreal classification was used in CD patients.¹⁶ The IBD disease status was evaluated based on the endoscopic disease activity and clinical activity within three months of dysplasia detection. The disease activity of UC was evaluated using the Mayo score, and the endoscopic disease activity was evaluated using the Mayo endoscopic score (MES).^{17,18} In CD patients, the disease activity was assessed using the Crohn's Disease Activity Index¹⁹ and the endoscopic disease activity was evaluated using the Simple Endoscopic Score for Crohn's Disease.²⁰ In addition, this study assessed the types of medications used and whether there were any changes in IBD treatment after the adenoma diagnosis.

3. Assessment and management of polyps

1) Definition of polyps

ACRN was defined as an adenocarcinoma or advanced adenoma. Advanced adenoma included adenoma ≥ 10 mm or with tubulovillous/villous histology or HGD.^{21,22}

2) Characteristics of polyps and diagnostic tools

The lesions were classified as visible or invisible. In the case of visible lesions, the morphology of the polyps was classified as pedunculated (Ip), subpedunculated (Isp), sessile (Is), slightly elevated (O-IIa), flat (O-IIb), slightly depressed (O-IIc), excavated (O-III), or no visible lesion.²³ The lesions were divided into polypoid (Ip, Isp, and Is) and non-polypoid (IIa, IIb, IIc, III, and invisible dysplasia). The size (mm), number, and location of polyps, as well as the presence of metachronous, colitis-associated, or sporadic lesions, were also investigated. Lesions found in areas with IBD-related chronic inflammation were defined as colitis-associated lesions; those unrelated to chronic inflammation were defined as sporadic lesions.

The endoscopic modalities used to detect dysplasia were evaluated, including standard white-light endoscopy high-definition WLE (HD-WLE), and pan-chromoendoscopy. Furthermore, this study investigated whether random biopsies or targeted biopsies detected the lesions; if the lesions were diagnosed by random biopsy, they were defined as invisible lesions based on the SCENIC consensus.²⁴

3) Treatment for polyps

The treatment method was also evaluated. A physician made decisions based on the lesion characteristics and patient risk. Endoscopic mucosal resection or endoscopic submucosal dissection was considered for lesions with distinct borders based on the decision of the endoscopist. In contrast, surgery was considered for endoscopically unresectable lesions and invisible dysplasia, and total proctocolectomy with ileal-pouch anal anastomosis was considered for HGD or CRC.^{25,26} For patients diagnosed with LGD that did not involve the rectum or had comorbidities, partial colectomy or segmental resection was considered and performed in consultation with the surgeon.²⁷

4. Statistical analysis

The variables are expressed as median (interquartile range [IQR]) or n (%). The baseline characteristics were compared using an independent Student's t-test (or Mann–Whitney U test) for continuous variables and the χ^2 test (or Fisher's exact test) for categorical variables. The disease status and polyp characteristics of patients with IBD were divided into "ACRN" and "no ACRN" groups and compared. Logistic regression analysis was used to analyze the independent predictors of the risk factors for advanced polyps. The odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated. The data were analyzed using the SPSS software (version 25.0; IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered significant.

RESULTS

1. Comparison of the baseline characteristics and disease status of ACRN and no-ACRN groups

Table 1 lists the baseline characteristics of the ACRN and no-ACRN groups. The median age of the patients was 57 years (IQR, 48–64 years), and 74.7% of patients were male. Four patients had PSC, one of whom developed ACRN. Despite no significant difference among the patients in whom index LGD was discovered during the study period, 33.3% of patients who developed ACRN had already been diagnosed with LGD. No significant differences in medication use or underlying diseases were observed between the patients with and without ACRN (Table 1).

Table 1. Baseline Characteristics of the Study Subjects

Variables	Total (n=166)	ACRN (n=12, 7.2%)	No ACRN (n=154, 92.8%)	p-value*
Age	57 (48–64)	54 (50–63)	57 (48–64)	0.864
Male sex	124 (74.7)	9 (75.0)	115 (74.7)	0.980
Accompanying PSC	4 (2.4)	1 (8.3)	3 (1.9)	0.165
Underlying disease	42 (25.3)	2 (16.7)	40 (26.0)	0.475
Hypertension	9 (5.4)	0 (0)	9 (5.8)	0.389
Diabetes	7 (4.2)	0 (0)	7 (4.5)	0.450
Cardiovascular disease	11 (6.6)	1 (8.3)	10 (6.5)	0.805
Liver disease	8 (4.8)	0 (0)	8 (5.2)	0.418
Malignancy	3 (1.8)	0 (0)	3 (1.9)	0.626
Others ^a	18 (10.8)	2 (16.7)	16 (10.4)	0.501
Family history of CRC	1 (0.6)	0 (0)	1 (0.6)	0.779
Operation ^b	6 (3.6)	1 (8.3)	5 (3.2)	0.363
Smoking	30 (18.1)	0 (0)	30 (19.5)	0.091
Type of IBD				0.098
Crohn's disease	29 (17.5)	0 (0)	29 (18.8)	
Ulcerative colitis	137 (82.5)	12 (100.0)	125 (81.2)	
Disease duration	11.48 (7.85–14.50)	11.63 (1.59–14.53)	11.48 (7.87–14.50)	0.143
Previous diagnosis of LGD	34 (27.7)	4 (33.3)	34 (27.2)	0.650
Medication				
5-ASA	150 (90.4)	11 (91.7)	139 (90.3)	0.874
Steroid	26 (15.7)	3 (25.0)	23 (14.9)	0.355
Immunomodulator	38 (22.9)	1 (8.3)	37 (24.0)	0.213
Anti-TNF	21 (12.7)	0 (0)	21 (13.6)	0.171
Other biologics ^c	5 (3.0)	0 (0)	5 (3.2)	0.526

Data are expressed as median (interquartile range) or number (%).

ACRN, advanced colorectal neoplasia; PSC, primary sclerosing cholangitis; CRC, colorectal cancer; IBD, inflammatory bowel disease; LGD, low-grade dysplasia; 5-ASA, 5-aminosalicylic acid; anti-TNF, antitumor necrosis factor.

^aCKD, hereditary spherocytosis; RA, Tuberculosis; infarction; AS, Parkinson's disease. ^bExcluded IBD-related bowel operation. ^cUstekinumab, vedolizumab, mirikizumab.

*p-value for comparing patients with and without ACRN.

Table 2. Disease Status of the Patients with Inflammatory Bowel Disease

Variables	Total (n=166)	ACRN (n=12, 7.2%)	No ACRN (n=154, 92.8%)	p-value*
Ulcerative colitis	137 (82.5)	12 (100.0)	125 (81.2)	
Disease extension				0.071
E2 ^a	99 (72.3)	6 (50.0)	93 (74.4)	
E3 ^b	38 (27.7)	6 (50.0)	32 (25.6)	
Mayo score	1.0 (0–3.0)	3.5 (2.0–6.0)	1.0 (0–2.0)	0.010
MES	1.0 (0–2.0)	2.0 (1.0–2.0)	1.0 (0–2.0)	0.383
Crohn's disease	29 (17.5)	0 (0)	29 (18.8)	
Disease location				-
L2 ^c	18 (62.1)	0 (0)	18 (62.1)	
L3 ^d	11 (37.9)	0 (0)	11 (37.9)	
Disease behavior				-
Inflammatory	18 (66.7)	0 (0)	18 (66.7)	
Strictureing	7 (25.9)	0 (0)	7 (25.9)	
Penetrating	2 (7.4)	0 (0)	2 (7.4)	
CDAI	72.15 (45.38–179.27)	0 (0)	72.15 (45.38–179.27)	
SES-CD	4.0 (0.25–11.25)	0 (0)	4.0 (0.25–11.25)	

Data are expressed as number (%) or median (interquartile range).

ACRN, advanced colorectal neoplasia; MES, Mayo endoscopic score; CDAI, Crohn's disease activity index; SES-CD, Simple endoscopic score for Crohn's disease.

^aLeft sided, ^bPancolitis, ^cIleocolonic, ^dColonic.

*p-value for comparing patients with and without ACRN.

Table 3. Characteristics of Index LGD and Comparison between Patients With and Without Advanced Neoplasia

Variables	Total (n=166)	ACRN (n=12, 7.2%)	No ACRN (n=154, 92.8%)	p-value*
Type of endoscopy				0.944
SD-WLE	51 (30.7)	4 (33.3)	47 (30.5)	
HD-WLE	114 (68.7)	8 (66.7)	106 (68.8)	
Panchromoendoscopy	1 (0.6)	0 (0)	1 (0.6)	
Targeted biopsy	153 (92.2)	12 (100.0)	141 (91.6)	0.294
Colitis associated lesion	56 (33.7)	10 (83.3)	46 (29.9)	<0.001
Location				0.498
Cecum	13 (7.8)	0 (0)	13 (8.4)	
Ascending colon	36 (21.7)	2 (16.7)	34 (22.1)	
Transverse colon	35 (21.1)	2 (16.7)	33 (21.4)	
Descending colon	25 (15.1)	1 (8.3)	24 (15.6)	
Sigmoid colon	38 (22.9)	4 (33.3)	34 (22.1)	
Rectum	19 (11.4)	3 (25.0)	16 (10.4)	
Morphology				0.610
Polypoid ^a	146 (88.0)	10 (83.3)	136 (88.3)	
Non-polypoid ^b	20 (12.0)	2 (16.7)	18 (11.7)	
Number of polyps (mean)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.420
Size of polyp (mm)	5.0 (3.0–6.5)	11.50 (7.25–16.75)	4.0 (3.0–6.0)	<0.001
Treatment modality				0.003
Endoscopic resection	152 (91.6)	8 (66.7)	144 (93.5)	
Close follow-up	14 (8.4)	4 (33.3)	10 (6.5)	

Data are expressed as number (%) or median (interquartile range).

ACRN, advanced colorectal neoplasia; SD-WLE, standard definition white-light endoscopy; HD-WLE, high-definition white-light endoscopy.

^aPolypoid lesions: Ip, Isp, and Is. ^bNon-polypoid lesion: IIa, IIb, IIc, III, No visible lesion (random biopsy).

*p-value for comparing patients with and without ACRN.

One hundred and thirty-seven patients with UC (82.5%) and 29 with CD (17.5%) were evaluated. Left-sided UC (E2) accounted for 72.3% of patients, and 27.7% had pancolitis (E3). Six of the 38 patients with pancolitis developed ACRN (15.8%), which was not significant but showed a higher tendency than that of patients with left-sided UC (6.06%, six of 99). The disease activity was significantly higher in the ACRN group (Mayo score, 3.5 [2.0–6.0] vs. 1.0 [0–2.0]; $p=0.010$), but the endoscopic activity was similar in UC patients (MES, 2.0 [1.0–2.0] vs. 1.0 [0–2.0]; $p=0.383$). ACRN did not develop in patients with CD, but most showed ileocolonic involvement (62.1%) and non-stricturing and non-penetrating behavior (66.7%) (Table 2).

2. Clinical features and outcomes of index LGD

From January 2010 to December 2019, LGD was detected in 166 patients with IBD, of whom 33.7% had colitis-associated LGD (56 cases). An endoscopic resection was performed in 152 cases (91.6%), and biopsy removal was the most common method (83 of 152, 54.6%), followed by an endoscopic mucosal resection (EMR) (57 of 152, 37.5%) and cold snaring (12 of 152, 7.9%). In patients with UC who developed ACRN, colitis-associated LGD on the index colonoscopy was more common than in those with sporadic LGD (83.3% vs. 29.9%; $p<0.001$). In addition, the median size of the index LGD was 11.50 mm (IQR, 7.25–16.75) in the ACRN group, which was significantly larger than that in the no ACRN group ($p<0.001$). A total of 66.7% of patients with UC were examined using HD-WLE, and all index LGD cases in the ACRN group were diagnosed using a targeted biopsy. No significant differences in the shape, location, or number of polyps were noted. In patients with UC in the ACRN group, 66.7% of those with index LGD underwent endoscopic removal, while 33.3% underwent close follow-up (Table 3).

ACRN developed in 12 cases (7.2%), with a median duration of 3.05 years (IQR, 0.73–3.63) after the LGD diagnosis. Among these cases, six, three, and three patients had large LGD, tubulovillous adenoma, and HGD, respectively. All ACRN cases occurred in patients with UC (12 of 137, 8.8%), with a median disease duration of 11.48 years (IQR, 7.85–14.50). The sigmoid colon was the most frequent location (66.7%), followed by the transverse colon (16.7%), ascending colon, and rectum (8.3%). The most common morphology was sessile (ls) (83.3%), with a median size of 11.50 mm (IQR, 7.25–

16.75) (Table 4). Among the patients who underwent an endoscopic resection, ACRN occurred in eight of 152 cases (5.3%) in a different area from the previous lesions. No cases of CRC were encountered during the follow-up period, but HGD was found in 25% of patients. Regarding the treatment of ACRN, four cases underwent an endoscopic resection (including EMR or endoscopic submucosal dissection [ESD]); one was removed surgically, and seven were lost to follow-up before receiving proper treatment. Azathioprine was initiated as part of the treatment in one patient who underwent an endoscopic resection. Although ACRN did not develop in patients with CD, they had fewer colitis-associated lesions than sporadic lesions compared to those with UC (UC, 36.5% vs. CD, 20.7%) (Data not shown).

3. Risk factors of ACRN

Univariate analysis of the logistic regression model revealed colitis-associated lesions (OR, 11.739; 95% CI, 2.474–55.692; $p=0.002$) and polyp size (OR, 1.131; 95% CI, 1.029–1.243; $p=0.010$) to be significant factors for ACRN. Variables including male sex, age, lesion characteristics, polyp size, and colitis-associated LGD significantly increased the risk of developing ACRN (OR, 10.516; 95% CI, 2.064–53.577; $p=0.005$).

Table 4. Characteristics of ACRN

Variables	Total (n=12)
Follow-up duration (years)	3.05 (0.73–3.63)
Number of surveillance colonoscopy	2.0 (1.0–3.0)
Location of polyp	
Ascending colon	1 (8.3)
Transverse colon	2 (16.7)
Sigmoid colon	8 (66.7)
Rectum	1 (8.3)
Morphology	
Polypoid lesion ^a	10 (83.3)
Non-polypoid lesion ^b	2 (16.7)
Size (mm)	11.50 (7.25–16.75)
Pathologic finding	
Tubular adenoma	6 (50.0)
Tubulovillous adenoma	3 (25.0)
Villous adenoma	0 (0)
High-grade dysplasia	3 (25.0)

Data are expressed as medians (interquartile ranges) or number (%). ACRN, advanced colorectal neoplasia.

^aPolypoid lesions: lp, lsp, and ls. ^bNon-polypoid lesion: lla, llb, llc, ill, No visible lesion (random biopsy).

Table 5. Logistic Analysis of Risk Factors for ACRN (Logistic Analysis)

Variable	Uni-variate analysis		Multi-variate analysis	
	p-value	OR (95% CI)	p-value	Adjusted OR (95% CI)
Male sex	0.980	1.017 (0.262–3.949)	0.730	1.298 (0.295–5.717)
Age	0.863	0.996 (0.955–1.039)	0.869	1.004 (0.960–1.049)
Accompanying PSC	0.204	4.576 (0.439–47.716)		
Disease extension (excluded E1)				
E2, Left sided		1.0 (Ref.)		
E3, Pancolitis	0.082	2.906 (0.875–9.656)		
Medication				
5-ASA	0.874	1.187 (0.143–9.843)		
Steroid	0.362	1.899 (0.478–7.545)		
Immunomodulator	0.240	0.287 (0.036–2.302)		
Previous diagnosis of dysplasia	0.726	1.250 (0.358–4.363)		
Characteristics of lesion				
Sporadic lesion		1.0 (Ref.)		
Colitis associated lesion	0.002	11.739 (2.474–55.692)	0.005	10.516 (2.064–53.577)
Number of polyps	0.441	0.534 (0.108–2.632)		
Size of polyp	0.010	1.131 (1.029–1.243)	0.086	1.085 (0.989–1.190)

ACRN, advanced colorectal neoplasia; OR, odds ratio; CI, confidence interval; PSC, primary sclerosing cholangitis; 5-ASA, 5-aminosalicylic acid.

Table 6. Risk Factors for ACRN in IBD Patients with Colitis-associated Lesion (n=56; Logistic Analysis)

Variable	Uni-variate analysis	
	p-value	OR (95% CI)
Age	0.884	1.003 (0.958–1.051)
Accompanying PSC	0.484	2.444 (0.200–29.936)
Disease extension (excluded E1)		
E2, Left sided		1.0 (Ref.)
E3, Pancolitis	0.777	1.222 (0.305–4.894)
Medication		
5-ASA	0.936	1.098 (0.114–10.571)
Steroid	0.978	0.980 (0.221–4.352)
Immunomodulator	0.252	0.282 (0.032–2.454)
Previous diagnosis of dysplasia	0.025	9.429 (1.330–66.863)
Number of polyps	0.744	0.738 (0.119–4.566)
Size of polyp	0.109	1.080 (0.983–1.187)

ACRN, advanced colorectal neoplasia; IBD, inflammatory bowel disease; OR, odds ratio; CI, confidence interval; PSC, primary sclerosing cholangitis; 5-ASA, 5-aminosalicylic acid.

(Table 5). Among the patients with colitis-associated lesions (n=56), a history of LGD was a significant risk factor for ACRN (OR, 9.429; 95% CI, 1.330–66.863; p=0.025) (Table 6).

DISCUSSION

The risk of ACRN in patients with IBD requires attention,

and many controversies remain regarding the diagnosis, treatment, and follow-up. This study investigated the frequency and risk factors of ACRN development after diagnosing LGD in Korean IBD patients. In this study, patients with colitis-associated LGD, particularly those with a history of LGD, had a higher risk of ACRN. This result underscores the importance of rigorous inflammation control in patients with IBD

and a history of LGD.

The mechanism for the development of CRC has been known as sporadic CRC of the “adenoma–carcinoma sequence”²⁸ and CA-CRC of “inflammation–dysplasia–carcinoma sequence”.²⁹ Sporadic CRC can also occur in patients with IBD,³⁰ and chronic inflammation may generate oxidative stress-induced DNA damage and develop CRC from a non-dysplastic inflamed epithelium to dysplasia.^{29,31} In CA-CRC, the extent and severity of intestinal inflammatory lesions are well-known risk factors.^{32–34} In addition, variables including PSC, older age, family history of CRC, and male sex are risk factors for CA-CRC.^{35,36} Unlike sporadic cancers, CA-CRC occurs at a younger age, is often located proximally, and presents synchronous lesions more frequently.³⁷

Several guidelines recommend the duration of CRC surveillance in patients with IBD based on the risk.^{6,38,39} An annual colonoscopy is recommended for high-risk patients with pancolitis, moderate-to-severe inflammation, dysplasia, strictures within the past five years, PSC, or a family history of CRC in first-degree relatives <50 years of age.^{4,6,24,38,39} In this study, high-risk patients with CRC were included, and patients with ulcerative proctitis and Crohn’s disease with less than 30% colonic involvement were excluded, making it suitable for investigating the course of CA-CRC. Furthermore, in this study, ACRN was diagnosed at a median follow-up of three years after LGD detection, and the median number of colonoscopies performed was two, indicating that examinations were conducted approximately once every one to two years. This frequent monitoring increases the likelihood of detecting LGD with larger sizes or HGD rather than cancer. In addition, the number of polyps discovered during endoscopic surveillance is important. In the present study, patients had between one and five polyps discovered at the index colonoscopy. Among them, one patient had five polyps, while 92.6% of patients had only one to two polyps, with no significant difference in the occurrence of ACRN ($p=0.622$). This was because there was only one patient with five polyps, which is insufficient for investigating the risk of ACRN occurrence based on the number of polyps. Therefore, further large-scale studies are necessary. Among the 12 patients with ACRN, four (33.3%) had a prior history of LGD, and all lesions originated from colitis-associated lesions. Therefore, if colitis-associated LGD is identified in a previous colonoscopy, subsequent colonoscopies should be performed within one to three years, according to the guidelines. On the other hand, further evidence

and recommendations for surveillance of sporadic neoplasia in patients with IBD are currently lacking.

Regarding the treatment of patients with IBD with dysplasia, small polypoid and non-polypoid visible lesions with clear margins can be removed with an endoscopic resection technique using biopsy removal or snares.⁵ Moreover, EMR or ESD has been used for larger lesions.⁴⁰ In particular, ESD using an endoknife is generally considered for large (>20 mm) lesions, particularly those with high-risk features and flat lesions.^{25,40} Recent guidelines recommend surveillance colonoscopy rather than colectomy after removing polypoid/non-polypoid dysplastic lesions that can be removed endoscopically.²⁴ Mohan et al.⁴¹ conducted a meta-analysis of 1,037 patients with IBD who underwent endoscopic resection of dysplasia and reported that the pooled risk after lesion removal was two per 1,000 person-years of follow-up. In the present study, the index LGD was removed by endoscopy in 91.6% of the patients, and no cases of recurrence or ACRN development occurred in the same area. This result could be explained by the high prevalence of sporadic LGD on index colonoscopy in this study. On the other hand, endoscopic resection is useful for small LGD, considering that no ACRN developed in the same lesion, irrespective of sporadic or colitis-associated LGD. Furthermore, the present study reported that ACRN developed in 7.2% of IBD patients with LGD diagnosed during previous surveillance in Korea, and endoscopic resections had been performed for most visible LGD cases (91.6%). A European study examining the incidence of ACRN in patients with UC and LGD reported ACRN in 33 (19.1%) out of 172 patients at a median 48-month follow-up.⁴² The incidence of ACRN in this study was relatively low compared to Western data. This may be because the duration of subject enrollment in this study was less than 10 years compared to 20 years in the previous study. In contrast, a nationwide cohort study of 4,284 patients with IBD collected from the Dutch National Pathology Registry showed that the cumulative incidence of subsequent advanced neoplasia was 3.6, 8.5, 14.4%, and 21.7% after one, five, 10, and 15 years, respectively.¹⁰ This can be regarded as a similar incidence rate, considering that the median follow-up period in the present study was 3.74 years. Nevertheless, additional large-scale studies will be needed as the number of patients in this study was small compared to other studies.

In addition, patients with colitis-associated lesions had a

significantly higher risk of ACRN (OR, 10.516; 95% CI, 2.064–53.577; $p=0.005$). Among them, patients with a history of previous LGD showed a high risk of ACRN (OR, 9.429; 95% CI, 1.330–66.863; $p=0.025$). Other studies have reported that invisible or endoscopic non-polypoid dysplasia is an independent risk factor for developing HGD or CRC in patients with UC.^{11,42} A meta-analysis³⁵ reported that LGD, strictures, PSC, post-inflammatory polyps, family history of CRC, and UC versus CD were the risk factors for ACRN according to univariate analysis. Multivariate analysis revealed histological inflammation as a risk factor, and the results of this study confirmed that inflammation is a major factor in ACRN. Furthermore, considering that all ACRNs in the present study were from colitis-associated lesions, these patients may require special care, and more active inflammation control is needed because persistent inflammation can increase the risk of dysplasia.

This study had several limitations. First, data heterogeneity occurred from the retrospective analysis of six different hospitals. On the other hand, significant differences in patient groups or treatment patterns were not expected, considering that all participating institutions are specialized institutions, such as IBD clinics or centers. Second, inconsistencies in pathological and endoscopic findings were noted, possibly because of variations among pathologists and endoscopists across different hospitals. For example, the pathologist may have interpreted the colitis-associated lesion as dysplasia. In addition, although IND was also examined in this study, no case of IND was encountered. Hence, the diagnosis of IND may vary according to the pathologist, so bias due to differences in interpretation cannot be excluded. In addition, being a multicenter study, there may have been variations in the endoscopic findings and follow-up periods, which could introduce potential selection bias. Furthermore, the follow-up period of 4.9 years may not provide sufficient data to determine the long-term risk of ACRN, highlighting the need for further research with extended follow-up. Nevertheless, this study is significant because it was the first in Korea to analyze the clinical features, progression, and risk factors of LGD in a relatively large number of centers. This study provides valuable insights by showing that the risk of ACRN in Korea is not higher than expected.

In conclusion, ACRN occurred at a median of 3.05 years in 7.2% of IBD patients with previous LGD, and an increased risk of colitis-associated cases was observed. Therefore, ad-

herence to surveillance guidelines and more careful examination are recommended in patients with colitis-associated LGD, particularly those with a previous history of dysplasia. Hence, studies with a larger number of patients and longer duration are needed.

REFERENCES

1. Thia KT, Loftus EV Jr, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol* 2008;103:3167-3182.
2. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. *N Engl J Med* 2015;372:1441-1452.
3. Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis* 2013;19:789-799.
4. Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;13:144-164.
5. Farraye FA, Odze RD, Eaden J, et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010;138:738-745.
6. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: Ulcerative colitis in adults. *Am J Gastroenterol* 2019;114:384-413.
7. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: Management of Crohn's disease in adults. *Am J Gastroenterol* 2018;113:481-517.
8. Mooiweer E, van der Meulen-de Jong AE, Ponsioen CY, et al. Incidence of interval colorectal cancer among inflammatory bowel disease patients undergoing regular colonoscopic surveillance. *Clin Gastroenterol Hepatol* 2015;13:1656-1661.
9. Shah SC, Itzkowitz SH. Colorectal cancer in inflammatory bowel disease: Mechanisms and management. *Gastroenterology* 2022;162:715-730.e3.
10. De Jong ME, Van Tilburg SB, Nissen LHC, et al. Long-term risk of advanced neoplasia after colonic low-grade dysplasia in patients with inflammatory bowel disease: A nationwide cohort study. *J Crohns Colitis* 2019;13:1485-1491.
11. Pekow JR, Hetzel JT, Rothe JA, et al. Outcome after surveillance of low-grade and indefinite dysplasia in patients with ulcerative colitis. *Inflamm Bowel Dis* 2010;16:1352-1356.
12. Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* 1983;14:931-968.
13. Mahmoud R, Shah SC, Torres J, et al. Association between indefinite dysplasia and advanced neoplasia in patients with inflammatory bowel diseases undergoing surveillance. *Clin Gastroenterol Hepatol* 2020;18:1518-1527.e3.
14. Choi CH, Jung SA, Lee BI, Lee KM, Kim JS, Han DS. Diagnostic

- guideline of ulcerative colitis. *Korean J Gastroenterol* 2009;53:145-160.
15. Ye BD, Jang BI, Jeon YT, Lee KM, Kim JS, Yang SK. Diagnostic guideline of Crohn's disease. *Korean J Gastroenterol* 2009;53:161-176.
 16. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;55:749-753.
 17. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008;14:1660-1666.
 18. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;317:1625-1629.
 19. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;70:439-444.
 20. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004;60:505-512.
 21. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for follow-up after colonoscopy and polypectomy: A consensus update by the US multi-society task force on colorectal cancer. *Gastrointest Endosc* 2020;91:463-485.e5.
 22. Jung YS. Summary and comparison of recently updated post-polypectomy surveillance guidelines. *Intest Res* 2023;21:443-451.
 23. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003;58(6 Suppl):S3-43.
 24. Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R; SCENIC Guideline Development Panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastroenterology* 2015;148:639-651.e28.
 25. Wijnands AM, Mahmoud R, Lutgens MWMD, Oldenburg B. Surveillance and management of colorectal dysplasia and cancer in inflammatory bowel disease: Current practice and future perspectives. *Eur J Intern Med* 2021;93:35-41.
 26. Øresland T, Bemelman WA, Sampietro GM, et al. European evidence based consensus on surgery for ulcerative colitis. *J Crohns Colitis* 2015;9:4-25.
 27. Bemelman WA, Warusavitarne J, Sampietro GM, et al. ECCO-ESCP consensus on surgery for Crohn's disease. *J Crohns Colitis* 2018;12:1-16.
 28. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990;61:759-767.
 29. Frick A, Khare V, Paul G, et al. Overt increase of oxidative stress and DNA damage in murine and human colitis and colitis-associated neoplasia. *Mol Cancer Res* 2018;16:634-642.
 30. Choi CH, Rutter MD, Askari A, et al. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: An updated overview. *Am J Gastroenterol* 2015;110:1022-1034.
 31. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 2004;287:G7-17.
 32. Khan MA, Hakeem AR, Scott N, Saunders RN. Significance of R1 resection margin in colon cancer resections in the modern era. *Colorectal Dis* 2015;17:943-953.
 33. Stidham RW, Higgins PDR. Colorectal cancer in inflammatory bowel disease. *Clin Colon Rectal Surg* 2018;31:168-178.
 34. Hnatyszyn A, Hryhorowicz S, Kaczmarek-Ryś M, et al. Colorectal carcinoma in the course of inflammatory bowel diseases. *Hered Cancer Clin Pract* 2019;17:18.
 35. Wijnands AM, de Jong ME, Lutgens MWMD, Hoentjen F, Elias SG, Oldenburg B; Dutch Initiative on Crohn and Colitis (ICC). Prognostic factors for advanced colorectal neoplasia in inflammatory bowel disease: systematic review and meta-analysis. *Gastroenterology* 2021;160:1584-1598.
 36. Lazaridis KN, LaRusso NF. Primary sclerosing cholangitis. *N Engl J Med* 2016;375:1161-1170.
 37. Axelrad JE, Lichtiger S, Yajnik V. Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment. *World J Gastroenterol* 2016;22:4794-4801.
 38. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;68(Suppl 3):s1-s106.
 39. Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017;11:649-670.
 40. Saito Y, Otake Y, Sakamoto T, et al. Indications for and technical aspects of colorectal endoscopic submucosal dissection. *Gut Liver* 2013;7:263-269.
 41. Mohan BP, Khan SR, Chandan S, et al. Endoscopic resection of colon dysplasia in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Gastrointest Endosc* 2021;93:59-67.e10.
 42. Choi CH, Ignjatovic-Wilson A, Askari A, et al. Low-grade dysplasia in ulcerative colitis: risk factors for developing high-grade dysplasia or colorectal cancer. *Am J Gastroenterol* 2015;110:1461-1471; quiz 1472.