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Low-Grade Dysplasia in Ulcerative Colitis: Risk Factors for Developing High-Grade Dysplasia or Colorectal Cancer

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OBJECTIVES: The aim of this study was to identify risk factors associated with development of high-grade dysplasia (HGD) or colorectal cancer (CRC) in ulcerative colitis (UC) patients diagnosed with low-grade dysplasia (LGD).

METHODS: Patients with histologically confirmed extensive UC, who were diagnosed with LGD between 1993 and 2012 at St Mark's Hospital, were identified and followed up to 1 July 2013. Demographic, endoscopic, and histological data were collected and correlated with the development of HGD or CRC.

RESULTS: A total of 172 patients were followed for a median of 48 months from the date of initial LGD diagnosis (interquartile range (IQR), 15–87 months). Overall, 33 patients developed HGD or CRC (19.1% of study population; 20 CRCs) during study period. Multivariate Cox proportional hazard analysis revealed that macroscopically non-polypoid (hazard ratio (HR), 8.6; 95% confidence interval (CI), 3.0–24.8; $P<0.001$) or invisible (HR, 4.1; 95% CI, 1.3–13.4; $P=0.02$) dysplasia, dysplastic lesions ≥1 cm in size (HR, 3.8; 95% CI, 1.5–13.4; $P=0.01$), and a previous history of "indefinite for dysplasia" (HR, 2.8; 95% CI, 1.2–6.5; $P=0.01$) were significant contributory factors for HGD or CRC development. Multifocal dysplasia (HR, 3.9; 95% CI, 1.9–7.8; $P<0.001$), metachronous dysplasia (HR, 3.5; 95% CI, 1.6–7.5; $P=0.001$), or a colonic stricture (HR, 7.4; 95% CI, 2.5–22.1; $P<0.001$) showed only univariate correlation to development of HGD or CRC.

CONCLUSIONS: Lesions that are non-polypoid or endoscopically invisible, large (≥1 cm), or preceded by indefinite dysplasia are independent risk factors for developing HGD or CRC in UC patients diagnosed with LGD.

INTRODUCTION

The management of dysplasia arising in patients with ulcerative colitis (UC) is challenging. This is particularly pertinent in patients with low-grade dysplasia (LGD)—the most common type of dysplasia detected in surveillance programs—as its natural history of progression to colorectal cancer (CRC) is poorly understood. Indeed, the reported risk of CRC associated with LGD varies greatly between studies (1–9). While observed variation in cancer risk may simply reflect differences in methodology and population, there are several other important factors that may also have influenced outcomes. These include poor interobserver agreement in grading dysplasia among histopathologists (10,11), difficulty in reliably distinguishing colitis-associated dysplasia from sporadic adenomas (12), and difficulty in detecting sub-

tle dysplastic lesions. These challenges may reflect the fact that LGD is unlikely to be a single entity. Rather, it is likely that there is a wide spectrum of malignant potential in the variety of LGD lesions that we encounter in clinical practice.

In 1981, Blackstone *et al.* (3) first introduced the term "dysplasia-associated lesion or mass." Unfortunately, the definition of dysplasia-associated lesion or mass is not clear and often used to describe a wide range of lesions, ranging from a small, discrete polyp detected in a diseased segment to a large irregular mass. However, it is important to differentiate these lesions, as their malignant potential may vary significantly. For example, it is becoming increasingly clear that the risk of CRC is low following endoscopic resection of "adenoma-like" lesions arising in patients with UC (13–16).

The challenge is, of course, identifying patients whose LGD lesion has a high risk of developing advanced neoplasia from those who are at low risk. Although earlier studies demonstrated the efficacy of endoscopic removal of discrete adenomatous lesions without further significant cancer risk, patients who underwent early colectomy were typically excluded from these analyses and their characteristics are poorly understood (13–15). However, this is an important group to consider, as many patients in this group represent those who were *clinically* judged to be at a high risk and hence were offered colectomy early in their follow-up.

As one of the ultimate goals of managing LGD is the prompt recognition of high-risk lesions that warrant surgical intervention from those that can be managed appropriately endoscopically, there is a need for a study to assess full spectrum of patients diagnosed with LGD to characterize features associated with progression to more advanced neoplasia.

To fulfill this need, in this study we investigated data collected from the UC surveillance program at a large tertiary center in the United Kingdom (UK), with the aim of identifying potential risk factors that could be used to identify patients with a diagnosis of LGD who have a high risk of developing high-grade dysplasia (HGD) or CRC.

METHODS

Surveillance program

St Mark's Hospital is a tertiary referral center in the UK and established the UC surveillance program in 1971. Patients with endoscopic and histological evidence of UC proximal to the splenic flexure were offered surveillance colonoscopies every 1 to 2 years from 8 to 10 years after onset of UC symptoms.

At each colonoscopy, ~8 to 12 segmental random biopsies were taken, with multiple targeted biopsies from any suspicious area of mucosa. In more recent years (from 2003 onward), there has been a gradual increase in number of surveillance procedures performed with chromoendoscopy (CE), where pancolonic dye spray is used to highlight abnormal mucosa for targeted biopsies. By 2011, approximately one in two surveillance colonoscopies were performed using this technique.

Each episode of dysplasia was graded according to the 1983 Inflammatory Bowel Disease Dysplasia Morphology Study group

classification (17) and was independently reviewed by two experienced gastrointestinal pathologists at the time of diagnosis in accordance with the standard hospital policy.

Patient identification and inclusion criteria

Patients with histologically confirmed extensive UC who had at least one episode of LGD detected between 1 January 1993 and 31 December 2012 were retrospectively identified from St Mark's Hospital's Inflammatory Bowel Disease (IBD) database (registered with National Research Ethics Committee and Northwest London Hospitals NHS Trust; reference number, 09/H0717/4).

Patients who had at least one follow-up colonoscopy or surgical intervention after initial LGD diagnosis were included in the study. Patients whose first episode of dysplasia was found incidentally in their colectomy specimen (performed for reasons other than dysplasia/CRC, e.g., medically refractory colitis) were excluded. Patients who were referred to our institution with dysplasia diagnosis already established elsewhere were not considered in this study.

Data collection

Data were collected from the hospital's IBD database, clinical notes, surgical case notes, and endoscopy and histology reports. Detailed information on how variables were categorized is described below:

1. ***Macroscopic shape of the dysplastic lesion:*** patients were categorized based on the first episode of LGD, according to the lesion shape noted at colonoscopy.

    a. *Polypoid:* Paris type 0–I lesions (discrete pedunculated or sessile). Examples of polypoid lesions are shown in **Figure 1a–c**.
    b. *Nonpolypoid:* Paris type 0–II (macroscopically *visible* flat, slightly elevated or depressed), 0–III (excavated), irregular, or plaque-like lesions. The lesions of any shape with evidence of dysplasia in surrounding mucosa were considered as nonpolypoid. Examples of nonpolypoid lesions are shown in **Figure 1d–f**.
    c. *Invisible:* absence of documented endoscopic abnormalities. If the visible lesion was detected on subsequent examinations within 12 months, categorization was based on the visible lesion found.
    d. When more than one type of lesions were found, the categorization was based on presence of a lesion with maximal carcinogenic potential, in order of nonpolypoid, invisible, and polypoid lesions. This hierarchy was based on their risk of developing HGD or CRC in our preliminary analysis on patients with a single dysplastic lesion only: the hazard ratios (HRs) of patients with nonpolypoid or invisible lesions were 16.5 (95% confidence interval (CI), 5.8–46.5) and 6.8 (95% CI, 2.2–21.1), respectively, compared with those with polypoid lesions (reference category).

2. ***Lesion size:*** each case was categorized based on *presence* or *absence* of the visible dysplastic lesion ≥1 cm in size at colono-
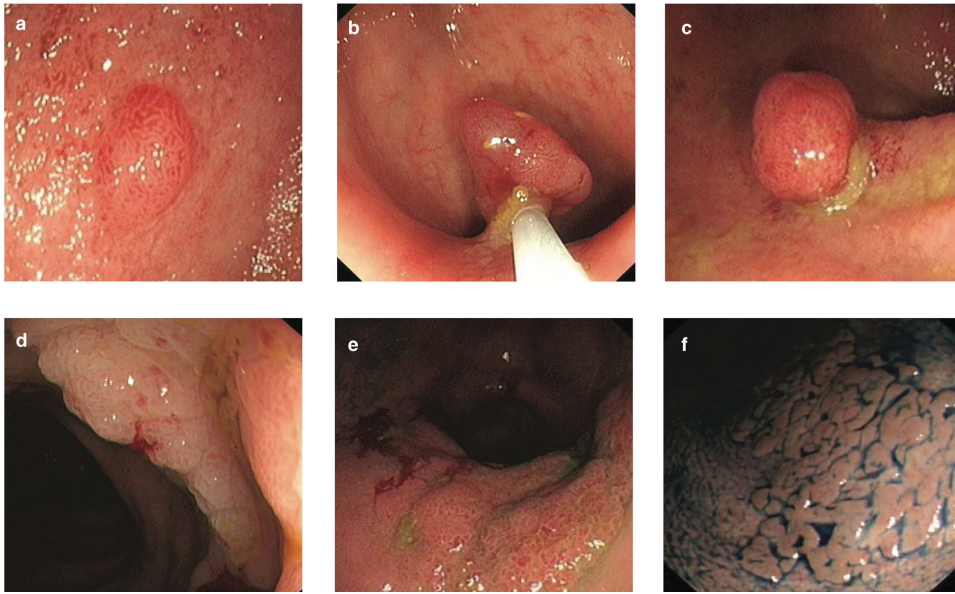
Figure 1. Lesion shape categorization. Discrete sessile (**a**), pedunculated (**b**), or sub-pedunculated lesions (**c**) that were well circumscribed from the surrounding mucosa were classified as "polypoid" LGD. Superficially raised (**d** and **e**), visible flat (**f**), irregular, or plaque-like lesions were classified as "nonpolypoid" LGD.

scopy. When multiple dysplastic lesions were found, the categorization was based on the largest lesion present.

3. ***Exposure to chromoendoscopy (CE):*** the patient was considered exposed to CE if he/she had one or more procedures performed using CE at the time of or after the diagnosis of initial LGD.

4. ***Multifocal LGD:*** if dysplasia was found in more than one location, the case was considered as multifocal.

5. ***Metachronous LGD:*** the patient was considered to have metachronous dysplasia if he/she had more than one episode of LGD during their surveillance.

6. ***Other colonoscopic features:*** data on the presence or absence of a documented episode of the following colonoscopic appearances were collected: backwash ileitis, colonic stricture, postinflammatory polyp, scarring, a shortened colon, tubular appearance, featureless colon, and presence of severe macroscopic inflammation. Data on the quality of bowel preparation and the experience level of endoscopist performing the procedure were also documented (i.e., consultant, trainee, or nurse endoscopist).

7. ***Microscopic inflammation around the LGD:*** the data on the presence or absence of histological active or chronic inflammation around the site of dysplasia were documented.

8. ***Family history of CRC:*** the patient was considered to be positive if he/she had either first- or second-degree relatives who had CRC at any age.

9. ***Primary sclerosing cholangitis (PSC):*** the patient was considered positive only if the diagnosis was confirmed radiologically or histologically.

10. ***Exposure to 5-aminosalicylate or immunosuppressant:*** patients were categorized into three groups depending on the duration of exposure to 5-aminosalicylate or immunosup-

pressant since the time of earliest documented use—never, up to 10 years, or >10 years.

Study end point

The study end point was defined as development of HGD or CRC during surveillance or at colectomy up to 1 July 2013. If the patient had not developed HGD or CRC, they were censored at the earliest of: the time of last surveillance colonoscopy, colectomy, or 1 July 2013.

Statistical analysis

The data analysis was performed using the SPSS statistical software (version 20, IBM, Armonk, NY). All continuous variables are reported as medians with interquartile ranges (IQRs). The study end point was examined using Kaplan–Meier and Cox proportional hazards methods with right-censored data. As 24 potential predictors were being tested against two outcomes, a Bonferroni-adjusted significance level of 0.002 was used to select variables to be entered into the multivariate model to minimize the possibility of type 1 error.

RESULTS

Study population

A total of 201 patients were diagnosed with LGD between 1 January 1993 and 31 December 2012. Of these, 15 patients were excluded as they withdrew from the surveillance program before their next scheduled surveillance for following reasons: death (5 patients, all unrelated to CRC), defaulted/patient choice (8 patients), and transferred to another institution (2 patients). In addition, a further 10 patients were excluded as they were sched-

Table 1. Patient demographics (*n*=172)

Characteristic	Values
Male sex (%)	110 (64)
Age (median, IQR)	60 Years (51–67)
Duration of UC (median, IQR)	23 Years (12–32)
Extensive UC (%)	172 (100)
Median follow-up duration (IQR)	48 Months (15–87)
Median number of follow-up colonoscopy (IQR)	3 Per patient (1–6)
Median surveillance interval (IQR)	12 Months (7–16)
Median number of biopsies (IQR)	12 (9–17)

IQR, interquartile range; UC, ulcerative colitis.

uled to have first follow-up colonoscopy after the study end date. A further four patients were excluded as LGD was incidentally found in their surgical specimen from a colectomy performed for medically refractory disease. Thus, a total of 172 patients met the inclusion criteria.

The demographics of the study population is summarized in **Table 1**. LGD was more commonly detected in males (110, 16.0% of the male population under surveillance, *n*=687) compared with females (60, 11.2% of female population under surveillance, *n*=531; χ^2, *P*=0.02). The median age at initial LGD diagnosis was 60 years (IQR, 51–67 years) and the median duration of UC at initial LGD diagnosis was 23 years (IQR, 12–32 years).

After the initial LGD diagnosis, these 172 patients underwent a total of 707 additional follow-up surveillance procedures (median, 4 procedures per patient; IQR, 2–6), of which 628 were colonoscopies (median, 3 colonoscopies per patient; IQR, 1–6). The median surveillance interval was 12 months (IQR, 7–16 months). The median follow-up duration from initial LGD diagnosis to the study end point was 48 months (IQR, 15–87 months), with a cumulative patient-year follow-up duration of 850.4 years (**Table 1**).

Patient follow-up

Of the study population (*n*=172), 21 patients (12.2%) underwent immediate colectomy without further colonoscopy (i.e., with presurgical diagnosis of LGD only) in a median of 4 months (range, 2–8 months) after initial LGD diagnosis. Histological analysis of their surgical specimen revealed CRC in 7 (33.3%), HGD in 3 (14.3%), LGD in 8 (38.1%), and no neoplasia in 3 patients (14.3%).

The remaining 151 patients initially continued with endoscopic surveillance (87.8% of study population). Of these surveyed patients, 34 patients (22.5% of patients who remained in surveillance) were subsequently referred to colectomy, 31 of whom underwent colectomy at a median of 19 months (IQR, 11–35 months) after initial LGD diagnosis. Indications for colectomy were CRC in 4 (all had CRC in specimen), HGD in 11 (of whom 5 had CRC in specimen), and LGD in 15 patients (of whom 2 had CRC in specimen), and 1 patient had a colectomy for refrac-

tory colitis (specimen revealed no neoplasia). One patient who developed CRC was considered unfit for surgery and another two patients who developed HGD refused surgery and remained in surveillance.

The indications for colectomy and the maximal grade of neoplasia found in colectomy specimen for all patients who underwent colectomy during the study period (*n*=52) are shown in **Table 2**. Overall, when the indication for surgery was HGD, 45.5% (*n*=5/11) of the patients had CRC in their surgical specimen. For those who had colectomy for LGD, HGD or CRC was found in the colectomy specimens in 38.9% (*n*=14/36) of cases, 9 of which were CRC (9/36=25.0%; **Table 2**).

As of 1 July 2013, 104 patients (60.5% of study population) were still under endoscopic follow-up (median, 78.5 months per patient; IQR, 46–110 months). The surveillance was terminated before 1 July 2013 in 16 patients (9.3% of study population) because of death (7/16 patients, 1 of whom died of CRC without colectomy), age (3/16 patients), or patient choice (1/16 patients). The remaining 5 patients (2.9% of study population) defaulted on surveillance and were lost to follow-up.

Study end points

Overall, 33 patients (incidence rate, 38.8 per 1,000 patient-years) progressed to more advanced disease during the study period, with *n*=13 developing HGD (incidence rate, 15.3 per 1,000 patient-years) and *n*=20 developing CRC (incidence rate, 23.5 per 1,000 patient-years). Only 6 patients (30.0% of patients who developed CRC) had a detected HGD lesion before developing CRC. There was a wide range in time from LGD to development of HGD (median, 13.0 months; IQR, 4.0–37.0 months), or from LGD to CRC (median, 10.5 months; IQR, 4.0–36.0 months). HGD or CRC was detected either at the surveillance colonoscopy (*n*=16; 48.5% of progressors) or on colectomy (*n*=17; 51.5% of progressors).

Characteristics of LGD

For the majority of patients, the endoscopic shape classification of the first LGD lesion was polypoid (116 patients; 67.4% of study population), followed by nonpolypoid (39 patients; 22.7%) and endoscopically invisible lesions (16 patients; 9.3%). At the time of invisible dysplasia detection, bowel preparation was considered to be adequate or good in all cases, and the median number of random biopsies taken was 11 (IQR, 9–14), and this was not significantly different from the number of biopsies taken for visible lesions (median, 12; IQR, 9–17; Mann–Whitney *U*-test, *P*=0.4).

Thirty-six patients had multifocal dysplasia (20.9% of study population). Nonpolypoid lesions were notably more likely to be multifocal compared with polypoid lesions (19/39=48.7% for nonpolypoid vs. 16/116=13.8% for polypoid; Fisher's exact test, *P*<0.001). Metachronous LGD lesions were common (79 patients; 46.0% of study population). Nonpolypoid or invisible lesions were more likely to be metachronous compared with polypoid lesions (26/39=66.7% for nonpolypoid vs. 41/116=35.3% for polypoid, *P*<0.001; 12/16=75.0% for invisible vs. 41/116=35.3% for polypoid, *P*=0.005).

Table 2. Indications for colectomy and the maximal grade of neoplasia found in colectomy specimen

Indication for surgery (no. of patients)	Findings in surgical specimen				
	No dysplasia	Indefinite dysplasia	LGD	HGD	CRC (%)
Refractory colitis (1)	1	0	0	0	0 (0)
LGD (36)	8	1	13	5	9 (25.0)
HGD (11)	0	1	2	3	5 (45.5)
CRC (4)	0	0	0	0	4 (100.0)

CRC, colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Impact of chromoendoscopy on lesion detection

A total of 873 colonoscopies (including colonoscopies performed before initial LGD detection) were performed for 158 LGD patients who were on surveillance between 2003 and 2012, of which 285 were chromoendoscopy (32.6%). The detection rate (i.e., total number of lesions detected/total number of each type of colonoscopies performed on study cohort) of the nonpolypoid lesion was significantly higher in CE (45/285=15.8%) than white-light endoscopy (WLE; 46/588=7.8%; χ^2, $P<0.001$). There was no significant difference in the detection rate of polypoid lesions (17.5% for CE vs. 15.3% for WLE; $P=0.08$) and invisible lesions (1.8% for CE vs. 1.4% for WLE; $P=0.50$) between these two techniques.

Factors determining development of HGD or CRC

Univariate analysis. The results of univariate analysis of potential demographic, endoscopic, and histological risk factors for developing HGD or CRC are shown in **Tables 3–5**, respectively.

In contrast to patients with polypoid dysplasia, a significant risk of developing HGD or CRC was observed among those with nonpolypoid dysplasia (HR, 16.5; 95% CI, 6.8–39.8; $P<0.001$) or endoscopically invisible dysplasia (HR, 6.2; 95% CI, 2.1–18.4; $P=0.001$; **Table 4**). Patients with lesions ≥1 cm were more likely to develop HGD or CRC (HR, 10.0; 95% CI, 4.3–23.4; $P<0.001$) compared with those with lesions <1 cm (**Table 4**). In addition, metachronous dysplasia (HR, 3.5; 95% CI, 1.6–7.5; $P=0.001$), multifocal dysplasia (HR, 3.9; 95% CI, 1.9–7.8; $P<0.001$), previous history of indefinite dysplasia (HR, 5.0; 95% CI, 2.3–10.9; $P<0.001$), and a colonic stricture (HR, 7.4; 95% CI, 2.5–22.1; $P<0.001$) showed a strong correlation to the risk of HGD or CRC (**Tables 4** and **5**).

None of the other variables showed a significant association with risk of HGD or CRC, although a nonsignificant (at Bonferroni adjusted significance level of 0.002) trend toward the HGD or CRC development was observed with coexisting primary sclerosing cholangitis (HR, 3.8; 95% CI, 1.3–11.0; $P=0.01$), a shortened colon (HR, 2.9; 95% CI, 1.2–7.0; $P=0.02$), and active (HR, 2.1; 95% CI, 1.0–4.4; $P=0.03$) or chronic (HR, 3.8; 95% CI, 1.5–9.9; $P=0.01$) microscopic inflammation in the segment of LGD (**Tables 3–5**). In addition, patients who were exposed to at

Table 3. Univariate analysis of potential demographic factors associated with HGD or CRC

Variables	Number (%)	Hazard ratio (95% CI)	P value
Family history of CRC	20 (12)	0.7 (0.2–2.2)	0.5
Male sex	110 (64)	1.1 (0.5–2.2)	0.8
PSC	10 (6)	**3.8 (1.3–11.0)**	**0.01**
Duration of UC (years)			
<10	27 (16)	1	
10–29	96 (56)	1.0 (0.3–3.1)	0.9
>30	49 (28)	1.4 (0.5–4.5)	0.5
Age (years)			
20–39	10 (7)	1	
40–59	70 (40)	2.0 (0.3–15.0)	0.5
≥60	92 (53)	1.6 (0.2–12.0)	0.6
5-ASA (years)			
Never	22 (13)	1	
Up to 10	72 (42)	0.9 (0.3–2.7)	0.9
>10	78 (45)	0.9 (0.3–2.8)	0.9
Immunosuppressant (years)			
Never	109 (63)	1	
Up to 10	41 (24)	1.2 (0.6–2.6)	0.6
>10	22 (13)	0.6 (0.2–2.0)	0.4

5-ASA, 5-aminosalicylate; CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; PSC, primary sclerosing cholangitis; UC, ulcerative colitis. Statistically significant factors (P<0.002 after correcting for multiple testing) are shown in bold.

least one episode of chromoendoscopy had a slight reduction in their risk of HGD or CRC development but this was not significant after correction for multiple testing (HR, 0.4; 95% CI, 0.2–0.9; $P=0.02$; **Table 4**).

Multivariate analysis. A total of seven variables were entered into the multivariate model, the six variables that had a significance level $P<0.002$ in the univariate analysis and, furthermore,

Table 4. Univariate analysis of potential endoscopic factors associated with HGD or CRC

Variables	Number (%)[a]	Hazard ratio (95% CI)	P value
Lesion shape			
Polypoid	116 (67)	1	
Nonpolypoid	**39 (23)**	**16.5 (6.8–39.8)**	**<0.001**
Invisible	**16 (9)**	**6.2 (2.1–18.4)**	**0.001**
Large lesion (≥1 cm)	**60 (35)**	**10.0 (4.3–23.4)**	**<0.001**
Chromoendoscopy use	112 (65)	0.4 (0.2–0.9)	0.02
Endoscopist			
Consultant	119 (69)	1	
Trainee or nurse	46 (27)	1.3 (0.6–2.9)	0.5
Bowel preparation			
Good/adequate	156 (91)	1	
Poor	9 (5)	1.9 (0.6–3.9)	0.3
Backwash ileitis	18 (10)	2.2 (0.6–6.3)	0.3
Featureless colon	27 (16)	1.8 (0.8–4.1)	0.1
Pseudopolyps	108 (63)	0.8 (0.4–1.5)	0.4
Shortened colon	16 (9)	2.9 (1.2–7.0)	0.02
Scarring	114 (66)	0.8 (0.4–1.7)	0.6
Stricture	**6 (3)**	**7.4 (2.5–22.1)**	**<0.001**
Tubular colon	60 (35)	1.3 (0.6–2.5)	0.5

CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia.
[a]Variable categorization was not possible because of lack of documentation in following cases: lesion shape (1 case; 1% of study population), lesion size (2; 1%), experience of endoscopist (7; 4%), and quality of bowel preparation (7; 4%).
Statistically significant factors (*P*<0.002 after correcting for multiple testing) are shown in bold.

Table 5. Univariate analysis of potential histological factors associated with HGD or CRC

Variables	Number (%)[a]	Hazard ratio (95% CI)	P value
Metachronous	**79 (46)**	**3.5 (1.6–7.5)**	**0.001**
Previous indefinite dysplasia	**17 (10)**	**5.0 (2.3–10.9)**	**<0.001**
Multifocal	**36 (21)**	**3.9 (1.9–7.8)**	**<0.001**
Location[b]			
Proximal	74 (43)	1	
Distal	74 (43)	2.0 (1.0–4.4)	0.07
Both	13 (8)	—	—
Inflammation[a]			
Normal/quiescent	100 (58)	1	
Chronic	15 (8)	3.8 (1.5–9.9)	0.01
Active	56 (33)	2.1 (1.0–4.4)	0.03

CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia.
[a]Refers to microscopic inflammation in the segment of dysplasia. In one case this was unknown because of lack of documentation (1% of study population).
[b]Refers to location in relation to splenic flexure. The location of LGD was unknown in 11 invisible dysplasia cases (6%).
Statistically significant factors (*P*<0.002 after correcting for multiple testing) are shown in bold.

Table 6. Final multivariate model showing significant factors independently associated with HGD or CRC development

Variables	Hazard ratio (95% CI)	P value
LGD lesion shape		
Polypoid	1	
Nonpolypoid	**8.6 (3.0–24.8)**	**<0.001**
Invisible	**4.1 (1.3–13.4)**	**0.02**
Large lesion (≥1 cm)	**3.8 (1.5–13.4)**	**0.01**
Stricture	1.6 (0.5–5.4)	0.4
Metachronous	1.3 (0.5–3.4)	0.6
Previous indefinite dysplasia	**2.8 (1.2–6.5)**	**0.01**
Multifocal	1.8 (0.6–4.6)	0.3
Chromoendoscopy use	0.5 (0.3–1.0)	0.06

CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.
Statistically significant factors (*P*<0.05) are shown in bold.

exposure to chromoendoscopy (**Table 6**). The rational for the inclusion of the latter was to control for the gradual increase in the use of chromoendoscopy since 2002 that was likely to be the most significant change in the surveillance protocol that has occurred within the study period. The mean interval between each surveillance colonoscopy had not changed significantly over time (1.4 years in 1993–2002 vs. 1.1 years between 2003 and 2012; paired *T*-test, *P*=0.4).

After multivariate analysis, only nonpolypoid dysplasia (HR, 8.6; 95% CI, 3.0–24.8; *P*<0.001), endoscopically invisible dysplasia (HR, 4.1; 95% CI, 1.3–13.4; *P*=0.02), lesion size ≥1 cm (HR, 3.8; 95% CI, 1.5–13.4; *P*=0.01), and previous history of indefinite dysplasia (HR, 2.8; 95% CI, 1.2–6.5; *P*=0.01) remained as significant contributory factors to the HGD or CRC outcome (**Table 6**).

Factors determining development of CRC only

The analysis was repeated for only CRC cases as the outcome (*n*=20) (i.e., excluding HGD). In the univariate analysis,

nonpolypoid shape (HR, 18.8; 95% CI, 6.0–59.0; *P*<0.001), lesion size ≥1 cm (HR, 10.5; 95% CI, 3.5–32.0; *P*<0.001), colonic stricture (HR, 16.3, 95% CI, 4.8–54.9; *P*<0.001), and previous history of indefinite for dysplasia (HR, 5.8; 95% CI, 2.2–15.4; *P*<0.001) showed a significant association with development of CRC. None of the other variables were significant.
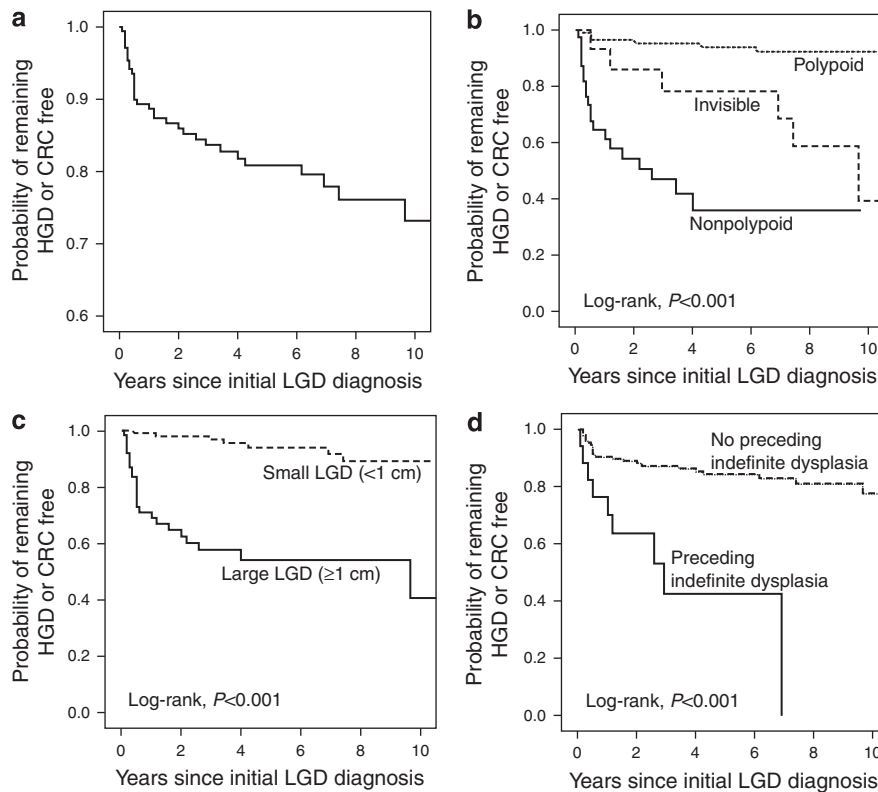
Figure 2. Kaplan–Meier plots showing cumulative risk of developing high-grade dysplasia (HGD) or colorectal cancer (CRC). (**a**) Overall cumulative risk. (**b**) Cumulative risk by low-grade dysplasia (LGD) lesion shape. (**c**) Cumulative risk by LGD lesion size. (**d**) Cumulative risk depending on the presence or absence of preceding indefinite dysplasia.

After multivariate analysis, only nonpolypoid shape (HR, 10.1; 95% CI, 2.4–42.8; P=0.002) and lesion size ≥1 cm (HR, 3.6; 95% CI, 1.04–12.6; P=0.04) remained as significant contributory factor to the CRC outcome. The previous history of indefinite for dysplasia (HR, 2.9; 95% CI, 0.99–8.6; P=0.053) and colonic stricture (HR, 3.7; 95% CI, 0.99–13.9; P=0.052) showed strong trend toward CRC outcome, but this was not statistically significant.

Rate of progression to HGD or CRC

Overall. Overall cumulative incidence of HGD or CRC development at 1 and 5 years after initial LGD diagnosis was 10.9% and 19.5%, respectively (mean annual hazard rate in first 5 years (HR), 4.7%, s.e., 0.9%; **Figure 2a**).

Based on individual risk factors. The cumulative incidence of HGD or CRC development based on lesion shape, size, and preceding dysplasia in the first 10 years from the date of initial LGD diagnosis is shown in **Table 7**. The cumulative incidence of HGD or CRC at 1 and 5 years after initial LGD was 3.5% and 6.0% for polypoid (HR, 1.3%; s.e., 0.6%), 6.7% and 21.9% for invisible (HR, 4.6%; s.e., 2.6%), and 36.6% and 65.2% for nonpolypoid LGD (HR, 18.2%; s.e., 3.6%), respectively (**Figure 2b**). When a large lesion (≥1 cm in size) was found, the cumulative incidence of

HGD or CRC at 1 and 5 years was 29.8% and 47.3% (HR, 12.6%; s.e., 2.4%), respectively (in contrast with a lesion <1 cm in size, for which these were 0.4% and 5.8% (HR, 1.2%; s.e., 0.5%); **Figure 2c**). If the first episode of LGD was preceded by indefinite dysplasia, the cumulative incidence of HGD or CRC at 1 and 5 years was 24.3% and 55.7% (HR, 16.0%; s.e., 5.1%), respectively. If the LGD was the first dysplasia, this was 9.4% and 15.8% (HR, 3.7%; s.e., 0.8%; **Figure 2d**), respectively.

Based on total number of risk factors. There was a significant positive correlation between the number of risk factors present and the cumulative risk of developing HGD or CRC (log-rank test, P<0.001; **Figure 3**). The cumulative incidence of HGD or CRC at 1 and 5 years after initial LGD was 0 and 1.8% for no risk factor (HR, 0.3%; s.e., 0.2%), 9.6 and 17.7% for one risk factor (HR, 4.9%; s.e., 1.8%), and 29.0 and 53.4% for two risk factors (HR, 13.6%; s.e., 3.3%). For those with three risk factors, cumulative risk of HGD or CRC development was 61.6% and 80.7% at 1 and 2 years, respectively (**Table 7**).

In patients who remained in surveillance. We performed same analysis excluding patients who underwent immediate colectomy (n=21). The cumulative incidence of HGD or CRC development based on lesion shape, size, preceding dysplasia, and the total number of these risk factors present in the first 10 years from

Table 7. The cumulative incidence of HGD or CRC development based on lesion shape, size, preceding indefinite dysplasia, and total number of these risk factors present in the first 10 years from the date of initial LGD diagnosis

Cumulative incidence of HGD or CRC (%)										
Years	1	2	3	4	5	6	7	8	9	10
Overall	10.9	13.6	16.7	17.5	19.5	19.5	22.3	24.3	24.3	27.1
By lesion shape										
Polypoid	3.5	3.5	4.6	4.6	6.0	6.0	8.0	8.0	8.0	8.0
Invisible	6.7	14.1	21.9	21.9	21.9	21.9	31.7	42.2	42.2	56.7
Nonpolypoid	36.6	46.7	54.2	58.8	65.2	65.2	65.2	65.2	65.2	65.2
By lesion size										
<1 cm	0.4	2.0	3.1	4.3	5.8	5.8	7.8	10.7	10.7	10.7
≥1 cm	29.8	36.2	43.7	43.7	47.3	47.3	47.3	47.3	47.3	59.0
Preceding indefinite dysplasia										
No	9.4	10.9	12.6	13.6	15.8	15.8	17.3	19.3	19.3	22.3
Yes	24.3	38.1	55.7	55.7	55.7	55.7	85.3	—	—	—
Total number of risk factors (shape, size, or preceding indefinite dysplasia)										
None	0.0	0.0	0.0	0.0	1.8	1.8	1.8	1.8	1.8	1.8
1	9.6	9.6	13.1	17.7	17.7	17.7	17.7	41.1	41.1	41.1
2	29.0	40.5	48.8	48.8	53.4	53.4	58.9	58.9	58.9	70.6
3	61.6	80.7	—	—	—	—	—	—	—	—

CRC, colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

the date of initial LGD diagnosis is shown in **Supplementary Table S1** and **Supplementary Figure S1–S2** online.

DISCUSSION

In this study, we performed a detailed analysis of HGD and CRC risk in a large number of UC patients diagnosed with LGD, taking their demographic, endoscopic, and histological characteristics into account. We have shown that UC patients with LGD that is non-polypoid, invisible, ≥1 cm in size, or preceded by indefinite dysplasia are at higher risk of developing HGD or CRC. In addition, we have described several other features that had a significant association with development of HGD or CRC in univariate analysis that may be useful in identifying high-risk patients.

Non-polypoid dysplastic lesions

In agreement with previous studies, our data shows that polypoid LGD lesions have a low risk of CRC (13,14,16,18). Polypoid lesions were the most common form of LGD found in our cohort and were removed endoscopically in the vast majority of cases (108/116 or 93.1%) suggesting that the majority of LGD lesions may be adequately managed without colectomy. It was previously shown that the risk of CRC was similar between adenoma-like lesions arising in diseased segment and sporadic adenoma occurring in disease-free segment (14,15), and furthermore studies have suggested that these lesions have
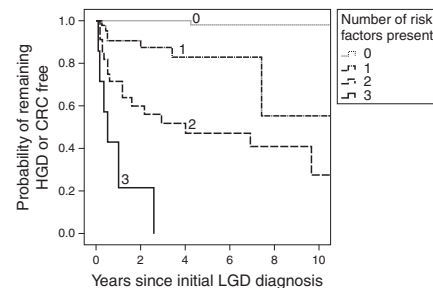

Figure 3. Kaplan–Meier plot showing the cumulative risk of high-grade dysplasia (HGD) or colorectal cancer (CRC) development depending on total number of risk factors present (i.e., any combinations of nonpolypoid or invisible low-grade dysplasia (LGD), LGD sized ≥1 cm, and/or preceding indefinite dysplasia).

genetic similarities (12,19). Thus, it is possible that adenoma-like lesions may simply represent sporadic adenomas that occur in patients with UC.

Patients with non-polypoid lesions, however, had a significantly higher cancer risk. Many of these lesions were not amenable for endoscopic resection (24 out of 39 or 61.5% of non-polypoid lesions), and were more likely to be multifocal compared with polypoid lesions. In our cohort, 13 out of 39 patients (33.3%) who initially had a LGD lesion that was considered nonpolypoid in shape later developed CRC. In addition, 6 of these

patients (6/13=46.2% of patients who developed CRC) had synchronous cancers in the surgical specimen. These lesions are an ominous finding and thus may require more aggressive management.

Of note, our results suggest that the CE was more effective at detecting non-polypoid lesions than WLE but the difference was minimal for polypoid lesions, and this is broadly in agreement with previous randomized controlled trial (20) and a recent meta-analysis (21). Given the significant risk of progression associated with nonpolypoid lesions, our data advocate the use of CE for early detection of these higher-risk lesions. As high-definition (HD) colonoscopy (i.e., HD colonoscope with HD-monitor) was only available since 2011 in our center, its efficacy could not be reliably assessed in our study. The value of HD WLE in detecting subtle dysplastic lesions compared with CE thus requires further dedicated study.

Large dysplastic lesions

It is well established that the malignant potential of a sporadic adenoma increases with size (22–24). However, the correlation of dysplastic lesion size and malignant potential in IBD is not well established. Our data suggest that lesions that are ≥1 cm have an approximately four-fold greater risk of progression compared with smaller lesions. This finding is in agreement with the data from IBD-free population where lesions >1 cm (or "advanced adenomas") were associated with ~3.6-fold increased risk of CRC compared with the general population (24). It was recently shown that the incomplete resection rate is higher for larger adenomas (10–20 mm) or non-conventional adenomas (25) and it is likely that a large non-polypoid dysplastic lesions in colitis are similarly more difficult to resect completely. Thus, it is important that advanced techniques are used when such lesion is being managed non-operatively, and if the complete resection cannot be achieved, colectomy may be advisable.

Although these results should provide a broad guidance in making management decisions, our data should be confirmed by prospective trials, as our retrospective study design limits adequate assessment for possible interobserver variability that may exist in classifying the lesion shape and size that was recently demonstrated to be only moderate (26).

Invisible dysplasia

Although most dysplastic lesions were endoscopically visible in our study, the presence of invisible dysplasia detected histologically within a random biopsy was a significant risk factor for HGD or CRC development in our multivariate analysis. Our results are in agreement with previous retrospective study from the US tertiary center (1) and a meta-analysis (27).

However, it should be noted that these studies were performed before the introduction of newer techniques, in particular, CE. It is difficult to know whether these "invisible" lesions were truly endoscopically invisible dysplasias or simply "missed" lesions.

In our data set, the incidence rate of invisible dysplasia in the recent decade was lower (7.4 per 1,000 patient-years between 2003 and 2012) compared with the previous decade (18.8 per 1,000 patient-years between 1993 and 2002), although this was not statistically significant (Fisher's exact, $P=0.07$). In contrast, the incidence rate of non-polypoid lesions increased by two-fold in the recent decade (36.2 per 1,000 patient-years between 2003 and 2012) compared with the previous decade (18.8 per 1,000 patient-years between 1993 and 2002).

These findings may suggest that invisible dysplasia is becoming a rare entity and is instead being increasingly detected as non-polypoid dysplasia, as improving endoscopic techniques and technologies allow detection of more subtle lesions. This may explain why patients with invisible dysplasia had a relatively high risk of progression to HGD or CRC. Nevertheless, it is important to confirm the nature of these invisible lesions in a dedicated study, as it is still possible that these are truly invisible lesions that are difficult to detect even with advanced techniques.

Thus, when an invisible dysplasia is detected, our current policy is to refer patients to an experienced endoscopist to have a repeat procedure performed with an advanced technique. Typically, HD CE is performed in an attempt to identify the lesion that was possibly missed in previous colonoscopy. In addition, segmental and targeted biopsies are taken as appropriate to ensure that any truly invisible lesions are not missed.

Preceding dysplasia

The previous history of indefinite for dysplasia showed a significant association with development of HGD or CRC. It is recognized that distinction between indefinite for dysplasia and LGD is challenging (11) and it was previously shown that indefinite dysplasia is frequently regraded to LGD after a dedicated review (28). Thus, one possible explanation is that these indefinite dysplasia may actually have been LGD. Furthermore, patients with metachronous LGD had high risk of developing HGD or CRC in a univariate analysis, suggesting that persistent dysplasia regardless of grade may increase the risk of progression. Patients with dysplasia with previous a history of any grade of dysplasia should therefore be closely monitored, and option for colectomy should be discussed with the patient if metachronous dysplasia develops persistently despite endoscopic resection.

Other risk factors

Several studies have documented a high rate of underlying CRC among patients with colonic stricture (29,30). In our study, four out of six patients with a colonic stricture had developed CRC. In particular, all three patients whose dysplasia was found within a stricture had advanced CRC. In the remaining patient, CRC (Dukes' B) was found proximal to the stricture, indicating that difficulty in access to the proximal colon may have been a contributing factor. Although the patient number is small in our cohort, the high proportion of patients who developed CRC indicates that finding a colonic stricture in patients with history of dysplasia should raise clinical suspicion for CRC.

Although multifocal dysplasia is generally perceived to be a high-risk feature, the evidence demonstrating this is scant (28,31). In our study, multifocal dysplasia showed a significant

association toward development of HGD or CRC in a univariate setting only, highlighting the importance of considering other independent risk factors in conjunction. For example, none of the patients with multifocal polypoid dysplasia (*n*=12) had developed HGD or CRC during a median of 63 months (IQR, 63–111 months).

Number of risk factors present and timing of colectomy

We observed a clear association between the numbers of risk factors present (i.e., lesion shape, size, and preceding indefinite dysplasia) and the risk of HGD or CRC development. Of note, patients with only one of these risk factors had 17.7% risk of progression at 5 years after initial LGD diagnosis.

Relatively low rate of progression observed in this group is perhaps not surprising, as it represent LGD cases that could be potentially removed endoscopically. For example, 18 patients (without preceding dysplasia) had their large polypoid LGD removed endoscopically (median size, 15 mm; IQR, 10–25 mm). During median follow-up of 33 months (IQR, 15–49 months), 2 of these patients developed CRC (both Dukes' A) in 6 and 24 months after resection and 1 patient developed HGD in 6 months (incidence rate, 45.5 per 1,000 patient-years).

Similarly, of 8 patients who underwent endoscopic resection for small (<1 cm) nonpolypoid lesions, 1 patient developed CRC (Dukes' A) in median follow-up of 44 months (IQR, 26–66 months; incidence rate, 26.8 per 1,000 patient-years). Thus, these data suggest that colectomy may not be always necessary for this group of patients, provided that the lesion can be resected in full with no evidence of dysplasia elsewhere in the colon. However, given the small number of cases, these data should be interpreted with caution.

In contrast, when patients had 2 risk factors, their risk of developing HGD or CRC exceeded 50% at 5 years following their initial LGD diagnosis. Furthermore, when all 3 risk factors were present, >80% of patients developed HGD or CRC within 2 years. Thus, these patients should be considered for early surgical intervention and counseling should be offered at the earliest opportunity.

Of note, only 30% (6/20) of CRCs were preceded by HGD in our cohort, indicating that a majority of CRCs were detected during colectomy performed for LGD (9/20; 45%) or at surveillance colonoscopy with last known worst dysplasia being LGD (5/20; 25%). Thus, our data suggest that the time when LGD is detected is likely to be the most appropriate time for assessing the risk associated with the lesion and offer surgical intervention for appropriate patients.

Limitations

Our study has limitations. First, it could be considered that our inclusion of patients who underwent early colectomy may have limited the accurate assessment of the natural history of LGD. This issue is particularly true for those patients with small polypoid LGD lesions who undergo early colectomy, as risk of HGD or CRC associated with such lesions may be underestimated. However, such cases are very rare in our experience: in our cohort,

only 1 patient out of 31 patients underwent colectomy within 12 months for LGD without having any of the aforementioned high-risk features (and no dysplasia or CRC was detected in the colectomy specimen). Moreover, excluding early colectomy patients entirely may potentially lead to underestimation of the risk associated with lesions with the aforementioned high-risk features as they often underwent colectomy within 12 months from initial LGD diagnosis (*n*=30/31, 14 of whom had HGD or CRC in the specimen).

Second, this study was conducted on a cohort from a tertiary referral center that includes a higher proportion of patients with more severe or complex disease. This has a potential impact on generalizability of our results, as the progression of LGDs in nontertiary centers may be different. For example, it is possible that dysplastic lesions studied in our work may represent those developed on background of more severe inflammatory drive, hence leading to more rapid progression. Furthermore, the rate of dysplasia detection and endoscopic removal may also vary significantly between centers.

CONCLUSION

In summary, we have revealed three important independent risk factors for HGD or CRC development in patients with LGD: lesion shape (non-polypoid or macroscopically invisible dysplasia), size of the lesion ≥1 cm, and history of previous indefinite for dysplasia. Patients with a LGD lesion who exhibit these risk factors have a high risk of developing HGD or CRC. Therefore, early surgical intervention should be considered in close discussion with the patient, particularly when more than one of these risk factors is present. Conversely, patients with small (<1 cm) polypoid lesion may be appropriately managed with endoscopic resection with close monitoring. Patients with multifocal dysplasia, previous history of *any* grade of dysplasia, and colonic stricture should be regarded as a considerable risk and intensive surveillance should be considered.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ Patients with ulcerative colitis (UC) who are diagnosed with low-grade dysplasia (LGD) have a significant risk of developing colorectal cancer (CRC). However, management of these patients is challenging because of marked variability in their rate of progression to more advanced neoplasia.

✓ There are little data on endoscopic and histological characteristics of LGD that are associated with a high risk of development of high-grade dysplasia (HGD) or CRC.

WHAT IS NEW HERE

✓ Patients with a LGD lesion that is non-polypoid in shape, endoscopically invisible, sized ≥1 cm or preceded by "indefinite for dysplasia" diagnosis have a high risk of developing HGD or CRC.

✓ Chromoendoscopy was more effective at detecting non-polypoid dysplasias than white-light endoscopy.

✓ If one or more of these risk factors are present, patients should be carefully counseled about their management options including colectomy.

✓ Conversely, patients with a small polypoid lesion and no other risk factors may be appropriately managed with close surveillance.

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