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Low risk of new dysplastic lesions in an inflammatory bowel disease population study with dye chromoendoscopy

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ABSTRACT

Background and study aims Rates of new dysplastic lesions or cancer progression after first dye chromoendoscopy in the era of high-definition endoscopy have yet to be determined.

Patients and methods A multicenter, population-based, retrospective cohort study was performed in seven hospitals in Spain. Patients with inflammatory bowel disease and fully resected (R0) dysplastic colon lesions under surveillance with high-definition dye-based chromoendoscopy were sequentially enrolled between February 2011 and June 2017, with a minimum endoscopic follow-up of 36 months. The aim was to assess the incidence of developing more advanced metachronous neoplasia by analyzing possible associated risk factors.

Results The study sample included 99 patients and 148 index lesions (145 low-grade dysplasia lesions and three high-grade dysplasia [HGD] lesions with a mean follow-up of 48.76 months [IQR: 36.34–67.15]). The overall incidence of new dysplastic lesions was 0.23 per 100 patient-years, 1.15 per 100 patients at 5 years and 2.29 per 100 patients at 10 years. A history of dysplasia was associated with a higher risk of developing any grade of dysplasia during follow-up ($P=0.025$), whereas left colon lesions were associated with a lower risk ($P=0.043$). The incidence of more advanced lesions at 1 year and 10 years was 1% and 14% respectively, with lesion size > 1 cm being a risk factor ($P=0.041$). One of the eight patients (13%) with HGD lesions developed colorectal cancer during follow-up.

Conclusions The risk of dysplasia progressing to advanced neoplasia and, specifically, the risk of new neoplastic lesions after endoscopic resection of colitis-associated dysplasia, are both very low.

Introduction

Patients with inflammatory bowel disease, both Crohn's disease (CD) and ulcerative colitis (UC), are at increased risk of colorectal cancer (CRC), namely colitis-associated colorectal cancer (CAC). The literature reveals a decrease in incidence and risk of CRC from the studies published in the 1950 s to those published in the last decade, as shown in a large meta-analysis published in 2014 [1]. This is partly due to a paradigm shift from old techniques, when most dysplasia was diagnosed on random biopsies of colon mucosa, to the advent of video endoscopy and newer endoscopic technologies that made most dysplasia dis-

covered in patients with IBD visible to investigators. However, in the last decade, newer advances in techniques in surveillance and management of dysplasia, such as high definition and chromoendoscopy, may have important implications for risk of CRC this population.

A Cochrane systematic review and meta-analysis [2] reported a lower incidence of cancer in patients with IBD undergoing surveillance compared to patients with IBD not undergoing surveillance. Chromoendoscopy has shown to increase the yield of dysplasia compared with standard-definition white-light colonoscopy [3]. Based on this evidence, national and international clinical and endoscopic guidelines recommend virtual chromoendoscopy (VCE) or dye chromoendoscopy (DCE) with high-definition white-light endoscopy for surveillance in patients with longstanding IBD with a high evidence level (1B) [4–7] and a recommendation grade of B. However, whether the identification of additional lesions with chromoendoscopy has had an impact on the risk of CRC in patients with IBD or it remains similar to the one reported in older studies is unknown.

Carcinogenesis in IBD follows the inflammation-dysplasia-cancer sequence from inflammation to indefinite, low-grade dysplasia (LGD), high-grade dysplasia (HGD), with some progressing to cancer [8]. Incidence of CAC associated with LGD or HGD in patients with IBD, therefore, is of special importance in management of these patients. Currently, the reported risk of CAC associated with LGD or HGD in patients with IBD varies greatly between published studies and cannot be defined precisely, although estimates for progression from LGD to a more advanced neoplasia range from 20 % to 30 % [9–11]. This variation may be partly due to the use of data that predate videoendoscopy and follow-up recommendations about patient risk factors that are based on data taken without high-definition endoscopies or chromoendoscopy surveillance.

There is a need to reassess the incidence of CAC associated with LGD or HGD in patients with IBD using data gathered exclusively with dye chromoendoscopy (DCE) with high-definition. In this context, an important risk factor is the morphology of the LGD lesion, because the progression risk seems to be different for LGD in elevated lesions and non-polypoid lesions (both graded with Paris Classification) [12, 13]; yet the risk for LGD in elevated lesions is similar to that in the general population and estimated to be 0.5 per 100 patients per year [14, 15], while the estimated risk of progression to CAC for non-polypoid LGD lesions is 1.35 per 100 patients per year [16, 17]. Many other clinical, endoscopic, and histological risk factors have been associated with CAC, as reported in several meta-analyses; the most significant ones are disease duration, disease extension, inflammation and severity, primary sclerosing cholangitis, family history of CRC, stricture disease, post-inflammatory polyps, and dysplasia [18].

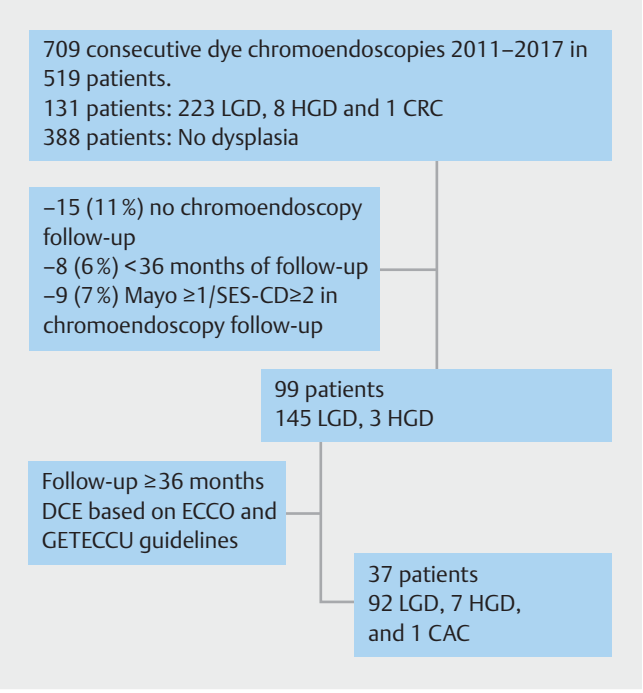
Given the improvements in visualization of morphology of LGD lesions associated with DCE with high-definition, this technique may also have an impact on assessment of this risk factor, as well as on other reported risk factors. In this scenario, in this study, we aimed to determine the incidence of new dysplastic lesions during DCE follow-up and, specifically, the incidence of developing more advanced metachronous neoplasia (HGD or CAC), as well as to analyze possible associated risk factors.

Patients and methods

This was a large multicenter, population-based, retrospective, long-term follow-up study conducted across seven different hospitals in Spain by the Castilla y León Inflammatory Bowel Disease Group (GEICYL). We retrospectively collected 232 dysplastic lesions from 131 patients following 709 consecutive DCE screening exams of 569 patients with longstanding IBD performed between February 2011 and June 2017. Patient data and lesion characteristics were first published in 2019 [19]. The inclusion criteria were left-sided or extensive UC or CD involving more than one-third of the colonic mucosa, disease duration >8 years, and clinical remission (partial Mayo score <3 for ulcerative colitis or Harvey Bradshaw <5 for CRC) excluding patients with moderate or severe endoscopic activity (Mayo ≥2 or SES-CD ≥5). Patients had signed informed consent forms permitting the use of their clinical data for research purposes. Chromoendoscopy was performed with indigo carmine (0.2–0.4 %) or methylene blue managed with a catheter spray and high-definition endoscopes, at both tertiary referral centers and local community hospitals. High-definition endoscopes with digital magnification but no optical magnification (Olympus Evis Exera II Cv-180 and Evis Exera III Cv-190) were used at all the hospitals. All the endoscopists were experts in performing dye chromoendoscopy and all the patients underwent chromoendoscopy of the whole colonic surface with targeted biopsies.

All dysplastic lesions identified were resected completely (R0) and the histological results were assessed. Endoscopic, histological, and clinical data were collected by electronic chart review. Fifteen patients (14 %) were lost to follow-up because no new chromoendoscopies were performed (mainly due to the COVID-19 pandemic over the last 2 years, and because five patients refused endoscopic follow-up), and eight patients were excluded with less than 36 months' follow-up and nine patients with endoscopic activity in DCE during follow-up. ▶ **Fig. 1** shows the study flowchart. Finally, we included 99 patients with 148 dysplastic lesions (145 LGD and 3 HGD) with a mean follow-up of 48.76 months (IQR: 36.34–67.15).

Dysplastic lesions were classified as LGD or HGD according to the 1983 IBD dysplasia morphology study group classification [20] and DCE follow-up was based on current European guidelines (ECCO) [4] and Spanish Working Group on CD and UC (GETECCU) consensus [7]. Lesion size was categorized according to the Paris classification [12, 13] by dividing the lesions into two groups: polypoid lesions including Paris classification 0-Is and 0-Ip and flat lesions (Paris 0-IIa, 0-IIb and mixed flat lesions 0-IIa/IIc). Any dysplastic lesions observed in random biopsies taken to assess histological healing were classified according to the SCENIC consensus [21] for invisible dysplasia. The incidence of advanced neoplasia was defined as the presence of HGD or CRC, found either during colonoscopy or in a surgical colectomy specimen. Persistence of dysplasia was de-



▶ **Fig. 1** Flowchart.

fined as the presence of LGD found during subsequent surveillance colonoscopies.

The aim of this study was to determine the incidence of new dysplastic lesions during DCE follow-up and, above all, the incidence of developing more advanced metachronous neoplasia (HGD or CAC) by analyzing possible associated risk factors.

Statistics

Data were collected and processed using Microsoft Office Excel and subjected to statistical analysis using IBM SPSS 19 statistical software after setting a 95 % confidence interval. The sample was subjected to a descriptive analysis to obtain means (standard deviation) or the frequency (percentage) according to the characteristics and distributions of the variables.

The relationship between dysplasia follow-up and the rest of the variables was analyzed using the chi-squared test; alternatively, Fisher's test was used if the conditions of applicability were not met for the chi-squared test. Finally, we calculated the statistical significance and risk (OR).

Results

A total of 99 patients with 148 dysplastic lesions (145 LGD and 3 HGD) were included. Patient characteristics are summarized in ▶ **Table 1**. Of the 85 patients with UC (86 % of the total sample), 59 (69 % of patients with UC) had pancolitis; 11 patients (11 % of the total sample) had CD involving more than one-third of the colonic mucosa. Regarding the associated risk factors for CAC, two patients had primary sclerosing cholangitis (2 % of the total sample), 10 had a family history of CRC (10 % of the total sample) and just nine had a history of dysplasia (9 % of the total sample).

▶ **Table 1** Baseline characteristics for included patients with dysplasia.

Patients (n = 99)		N (%)
Male	61 (62)	
Age at diagnosis	40 ± 13	
Diagnosis	Ulcerative colitis	85 (86)
	Pancolitis (E3)	59 (69)
	Crohn's disease	11 (11)
	Indeterminate colitis	3 (3)
Follow-up (months)	48.76 (36–67)	
Smoking status	Active	8 (12)
	Ex-smoker	25 (38)
	Non-smoker	32 (49)
PSC	2 (2)	
Pseudopolyps	40 (40)	
Family history of CRC	First degree	7 (7)
	Other degree	3 (1)
History of dysplasia	9 (9)	
	LGD	8 (8)
	HGD	1 (1)
Treatment	Oral 5-ASA	86 (87)
	IMM	35 (35)
	Anti-TNF	11 (11)
	Other biologics	2 (2)

PSC, primary sclerosing cholangitis; CRC, colorectal cancer; LGD, low-grade dysplasia; HGD, high-grade dysplasia; 5-ASA: mesalamine; IMM, immunomodulator.

Most of the dysplastic lesions (138) were < 1 cm across (93 %), half were polypoid (50 %), and 35 % were located in the right colon. Nearly all of the lesions (90 %) were en bloc resected, while 7 % were piecemeal resected (endoscopic mucosal resection, [EMR]). Lesion characteristics are summarized in ▶ **Table 2**.

Incidence of advanced neoplasia or persistence of dysplasia

At the end of follow-up, 37 patients developed 97 new dysplastic lesions (92 LGD, 4 HGD, and 1 CAC) and one patient developed multifocal invisible dysplasia (2 HGD). The overall incidence of new dysplastic lesions was 0.23 per 100 patient-years, 1.15 per 100 patients at 5 years and 2.29 per 100 patients at 10 years (▶ **Fig. 2**), and the incidence of more advanced lesions at 1 year and 10 years was 1 % and 14 % respectively. From another perspective, the probability of a patient with a history of dysplasia not developing a new lesion during follow-up with high-definition chromoendoscopy was 75 % at 3 years and 50 % at

▶ **Table 2** Characteristics of dysplastic index lesions and dysplasia during follow-up.

	Characteristics	Index lesionsn (%)	Dysplasia during follow-up n (%)
Elevated or flat lesion (n = 97)	> 1 cm	10 (7 %)	4 (4 %)
	< 1 cm	138 (93 %)	93 (96 %)
	Polypoid lesion	74 (50 %)	51 (53 %)
	Flat lesion	74 (50 %)	46 (47 %)
	Rectosigmoid	27 (18 %)	22 (23 %)
	Left colon	36 (24 %)	40 (41 %)
	Transverse colon	33 (22 %)	23 (24 %)
	Right colon	52 (35 %)	40 (41 %)
Dysplastic lesion or invisible dysplasia (n = 100)	LGD	145 (98 %)	92 (92 %)
	HGD	3 (2 %)	6 (6 %)
	CAC	0 (0 %)	1 (1 %)

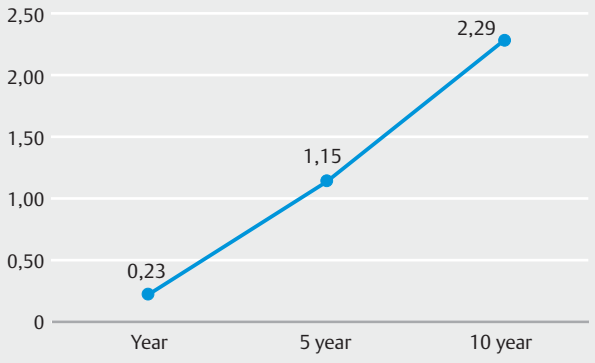
LGD, low-grade dysplasia; HGD, high-grade dysplasia; CAC, colitis-associated colorectal cancer.

4.7 years, as shown in ▶ **Fig. 3**. The most common location for new dysplastic lesions was the right colon (43.3 %), and nearly all were < 1 cm (96 %). ▶ **Fig. 4** shows that the index dysplastic lesions had a distribution, size, and Paris classification similar to the follow-up lesions.

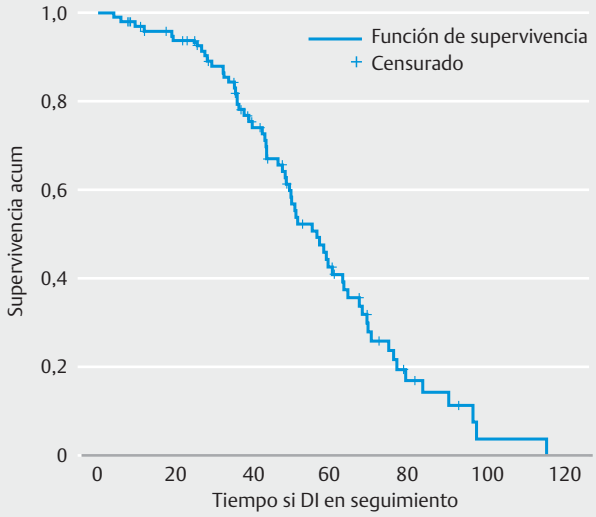
The patient who developed CAC did so over a flat lesion (Paris 0-IIa) > 1 cm, and their previous chromoendoscopy revealed a HGD lesion > 1 cm that underwent an R0 resection using EMR; both lesions affected the right colon. The two findings of invisible HGD were detected in a 42-year-old patient with extensive UC (E3) with no other risk factors except the findings in the chromoendoscopy of the index from the year before, namely an LGD in an elevated lesion (Paris 0-Is) < 1 cm from which random biopsies were taken for the diagnosis of histological screening. A panproctocolectomy with reservoir was performed and multifocal LGDs were observed in the surgical specimen. Three patients had HGD in the index lesion, all were Paris 0-IIb. One patient was treated directly with colectomy, another developed CAC in a flat lesion > 1 cm during follow-up, and the third, who had a high surgical risk, elected a conservative approach and developed LGD lesions during follow-up that were R0 resected without developing new HGD or CAC lesions. ▶ **Table 3** summarizes the characteristics of patients with HGD or CAC lesions in the index or follow-up lesion.

Risk factors for advanced neoplasia or persistence of dysplasia

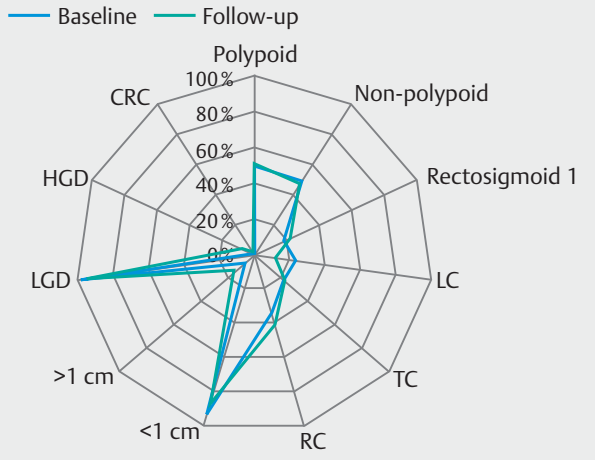
When analyzing risk factors for progression to HGD or CAC, lesion size > 1 cm was associated with a higher risk (OR of 12.29 [2.08–72.57] $P = 0.013$), whereas lesion size < 1 cm was a protective factor (OR 0.09 [0.01–0.65] $P = 0.013$). Neither location nor a history of dysplastic lesions was associated with more ad-



▶ **Fig. 2** Overall incidence of new dysplastic lesions.



▶ **Fig. 3** Probability that a new dysplastic lesion does NOT develop during follow-up.



▶ **Fig. 4** Characteristics of dysplastic index lesions and dysplasia during follow-up.

▶ **Table 3** Patients with HGD or CAC lesions in index DCE or during follow-up.

Patient	Disease (year of diagnosis)	Index lesion (Paris/localization)	Follow-up lesion (Paris/localization)	Outcome
1	CU E3 2007	LGD 0-Is TC < 1 cm	HGD 0-Is < 1 cm LC HGD 0-Ip > 1 cm RC	Surgery
2	CU E3 2011	LGD 0-Is TC < 1 cm LGD 0-Is RC > 1 cm	HGD 0-Is > 1 cm TC	DCE
3	CU E2 1995	LGD 0-IIb > 1 cm sigmoid	HGD 0-IIb > 1 cm	DCE
4	CU E3 1997	LGD 0-Is RC < 1 cm	Invisible HGD (2)	Surgery
5	CU E3 2008	HGD 0-IIb > 1 cm sigmoid	–	Surgery
6	CU E3 1996	HGD 0-IIa < 1 cm RC	LGD 0-Is DBG RC	DCE
7	CU E3 2008	HGD 0-IIb > 1 cm RC	CAC 0-IIb > 1 cm RC	Surgery

HGD, high-grade dysplasia; CAC, colitis-associated colorectal cancer; DCE, dye chromoendoscopy; LGD, low-grade dysplasia; LC, left colon; TC, transverse colon; RC, right colon.

vanced neoplasia. ▶ **Table 4** shows the results of our statistical analysis. Upon analyzing the risk factors for developing any grade of recurrent dysplasia during follow-up, only a personal history of dysplasia was associated with an OR of 6.66 [1.30–34.01] $P = 0.025$), whereas left colon lesions were associated with a lower risk, OR 0.35 [0.12–0.99] ($P = 0.043$). There was no association between lesion size, pseudopolyps, and the type of treatment and the risk of developing any grade of dysplastic lesion during follow-up.

Discussion

In dysplasia DCE follow-up in our study, at 1 year, 1%, and at 10 years, 14% of patients progressed to HGD or CAC. These percentages are much lower than those previously published by Choi et al. [9], who saw a rate of 10% at 1 year, but similar to those recently reported by Cremer et al. [17] who observed rates of 1.9% at 1 year. Perhaps the inclusion of high-quality baseline endoscopy with DCE favors these lower progression rates; however, it should be noted that while the probability of progression is low, it is sustained over time and increases to 14% at 10 years, hence the data support the need to continue with the screening program at shorter follow-up intervals for these patients. A second analysis of the data in high-risk patients who have already had a dysplastic lesion removed shows that the probability of NOT developing a new lesion during follow-up is 75% at 3 years and 50% at almost 5 years. This suggests that we can detect and visualize more lesions with these new endoscopic techniques compared to the standard-definition endoscopes we have been using for decades.

There is a lack of data in the literature to establish the rates of progression to CAC using either virtual or dye chromoendoscopy, plus there are several problems when analyzing the literature in this regard. First, published studies, which mainly focused on flat lesions detected by chromoendoscopy techniques, have described a highly variable R0 resection rate. Therefore, in the English meta-analysis [15], the included studies reported R0 resection rates that ranged from 40% to 100%, and there were even studies that did not specify the rates, making it very hard to subsequently estimate the progression to CAC. In our study, complete R0 resection of the lesions was performed in 100% of cases, and biopsies were also taken from the edges of the index lesions without detecting dysplasia in any of the cases [19]. Second, the evidence suggests that progression to dysplasia is greater in flat lesions, which we can currently view with high-definition endoscopy and chromoendoscopy, with a rate of around 0.5 per 100 patients per year progressing to HGD and CAC for resection of elevated lesions. This progression rate is similar to the incidence after polypectomy in patients without associated colitis [14]; subsequent studies in this subgroup of patients reported rates of progression to cancer of between 0% and 4.5% at 2 years and between 0% and 13.6% at 4 years [15]. Many of these studies did not differentiate between LGD or HGD lesions.

The resection rate for flat lesions in our initial study was 50%, and this variable was not associated with the increased progression of dysplasia in DCE follow-up (OR 0.86 [0.16–4.48] $P = 1.000$) or with the appearance of any new dysplastic lesions (OR 1.11 [0.49–2.52] $P = 0.786$). The small number of advanced dysplasias or CAC lesions probably means it is hard to find these differences in this specific high-risk population. Furthermore, unlike the study of Cremer et al., in which 86% of patients diagnosed with CAC had not undergone a previous colonoscopy screening [17], in our sample, all patients had chromoendoscopy with resection of at least one LGD lesion.

Although many studies have examined the risk factors for developing CAC, very few have assessed the risk of developing new dysplastic lesions or progression to a higher grade of dysplasia or CAC from previously LGD lesions and, in fact, non-polypoid lesions are the most consistent risk factor, having a risk ratio of 15 [9]. In the same study, lesions measuring ≥ 1 cm and the prior presence of indefinite dysplasia were also risk factors for progression. In our patients, among the risk factors described for progression to HGD or CAC, only lesion size ≥ 1 cm was a risk factor with an OR of 12.29 (2.08–72.57; $P = 0.013$) and, by contrast, lesions < 1 cm behaved as a protective factor OR 0.009 (0.01–0.65; $P = 0.041$). Pseudopolyps, a history of PSC, the type of lesion, and the treatment applied were not

▶ **Table 4** Univariate analysis of risk factors associated with any dysplastic lesion or more advanced lesion during follow-up.

Variable	Any dysplastic lesion		More advanced lesion (HGD/CRC)	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Pseudopolyps	0.65 (0.28–1.51)	0.322	1.51 (0.29–7.90)	0.683
Family history of CRC	2.59 (0.27–24.14)	0.646	–	–
Previous dysplastic lesion	6.66 (1.30–34.01)	0.025	2.12 (0.22–20.5)	0.444
Severe endoscopic activity	0.79 (0.13–4.54)	1.000		1.000
Treatment				
▪ Oral 5-ASA	2.28 (0.58–8.91)	0.359		1.000
▪ IMM	1.11 (0.47–2.58)	0.807	1.90 (0.36–9.99)	0.663
▪ Anti-TNF	0.90 (0.24–3.33)	1.000	1.66 (0.17–15.67)	0.516
▪ Other biologics	1.57 (0.09–26.32)	1.000	1.35 (0.14–12.57)	0.580
Type of lesions				
▪ Polypoid	0.95 (0.42–2.17)	0.912	1.44 (0.25–8.28)	1.000
▪ Non-polypoid	1.11 (0.49–2.52)	0.786	0.86 (0.16–4.48)	1.000
Size of lesion				
▪ <1 cm	1.26 (0.22–7.25)	1.000	0.09 (0.01–0.65)	0.041
▪ >1 cm	1.70 (0.46–6.30)	0.501	12.29 (2.08–72.57)	0.013
Location				
▪ Recto-sigma	0.49 (0.18–1.33)	0.162	0.54 (0.06–4.88)	1.000
▪ Left colon	0.35 (0.12–0.99)	0.043		0.185
▪ Transverse colon	2.00 (0.83–4.79)	0.117	1.16 (0.20–6.70)	1.000
▪ Right colon	1.97 (0.86–4.48)	0.105	1.38 (0.26–7.22)	0.696

HGD, high-grade dysplasia; CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; ASA, mesalamine; IMM, immunomodulators TNF, tumor necrosis factor.

risk factors (▶ **Table 4**). Perhaps the use of high-definition chromoendoscopy in the context of pseudopolyps will allow us to determine which lesions are dysplastic and require resection, something that was greatly limited before with the use of standard-definition, dyeless endoscopy.

Prior dysplasia, although not a risk factor for progression to HGD or CAC, was associated, with an OR of 6.66 (1.30–34.01; $P = 0.025$), with the development of more lesions of any type of dysplasia (LGD, HGD, or CAC) during follow-up. These results agree with those reported in the literature and which form the basis for current recommendations for closer monitoring in these patients (GETECCU – Spanish Working Group on Crohn's Disease and Ulcerative Colitis). We will have to investigate whether the presence of dysplasia by itself is an isolated risk factor for the development of CAC or signals a carcinogenic line associated with other individual genetic or molecular factors that are currently being researched, such as the field cancerization theory, RNA mutations, DNA, microsatellite instability, or hypermethylation phenomena [18].

One strength of our study is that it followed a multicenter, population-based design with series follow-up using VCE in patients in whom dysplasia was detected in a previously published population-based, prospective, and consecutive registry. It should be noted that all lesions were fully resected (R0 was 100 %) and the mean follow-up was more than 4 years.

Unfortunately, this was a retrospective study with a very low incidence of HGD or CAC lesions, so the data could not be used to analyze associated risk factors; however, we included a very large sample and subjects were treated at multiple hospitals. Therefore, new high-definition chromoendoscopy techniques may help us to visualize and resect more lesions, thus resulting in lower progression rates than those typically described with conventional endoscopy.

Conclusions

The rate of progression to HGD or CAC and recurrence of LGD lesions was low in our prospective series of DCE-monitored patients with LGD lesions, with lesion size > 1 cm being associated with an increased risk of progression. Prior dysplasia was a risk factor for new lesions with dysplasia but not for progression to HGD or CRC.

These extremely low rates of new dysplastic lesions and progression to HGD or CAC, thanks to the use of high-definition endoscopy and chromoendoscopy, could be used to redefine the endoscopic follow-up intervals for these high-risk patients.

Competing interests

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