Even non-experts identify non-dysplastic lesions in inflammatory bowel disease via chromoendoscopy: results of a screening program in real-life

Authors
Beatriz Sicilia Aladrén1, Yago González-Lama2, María García-Alvarado3, Mónica Sierra4, Jesús Andrés Barrio5, Vanesa Prieto Vicente6, Luis Hernández7, Benito Velayos8, Lara Arias Garcia1, Lucía Relea9, Patricia Suarez10, Ramón Atienza7, Mónica Vásquez7, Luis Fernández-Salazar6, Fernando Muñoz6, on behalf of GEICYL (group of inflammatory bowel disease of Castilla y León)

Institutions
1 Hospital Universitario de Burgos, Burgos, Spain
2 Hospital Universitario Puerta de Hierro, Madrid, Spain
3 Complejo Asistencial de Zamora, Castilla y León, Spain
4 Hospital Universitario de León, León, Spain
5 Hospital Universitario Río Hortega de Valladolid, Valladolid, Spain
6 Hospital Universitario de Salamanca, Castilla y León, Spain
7 Hospital Santos Reyes. Aranda de Duero, Castilla y León, Spain
8 Hospital Clínico Universitario de Valladolid, Valladolid, Spain

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Corresponding author
Beatriz Sicilia, MD, PhD, IBD Unit Cooordinator; Gastroenterology and Hepatology Department, Hospital Universitario de Burgos, Av Islas Baelares s/n 09006, Burgos 947281800, Spain
bsicilia4@gmail.com

ABSTRACT
Background and study aims Chromoendoscopy with targeted biopsy is the technique of choice for colorectal cancer screening in longstanding inflammatory bowel disease. We aimed to analyze results of a chromoendoscopy screening program and to assess the possibility of identifying low-risk dysplastic lesions by their endoscopic appearance in order to avoid histological analysis.

Materials and methods We retrospectively reviewed chromoendoscopies performed between February 2011 and June 2017 in seven Spanish hospitals in a standardized fashion. We analyzed the findings and the diagnostic yield of the Kudo pit pattern for predicting dysplasia.

Results A total of 709 chromoendoscopies (569 patients) were reviewed. Median duration of disease was 16.7 years (SD 8.1); 80.4% had ulcerative colitis. A total of 2025 lesions (3.56 lesions per patient) were found; two hundred and thirty-two lesions were neoplastic (11.5%) (223 were LGD (96.1%), eight were HGD (3.4%), and one was colorectal cancer (0.5%). The correlation between dysplasia and Kudo pit patterns predictors of dysplasia (≥III) was low, with an area under the curve of 0.649. Kudo I and II lesions were correctly identified with a high negative predictive value (92%), even by non-experts. Endoscopic activity, Paris 0-Is classification, and right colon localization were risk factors for dysplasia detection, while rectum or sigmoid localization were protective against dysplasia.

Conclusions Chromoendoscopy in the real-life setting detected 11% of dysplastic lesions with a low correlation with Kudo pit pattern. A high negative predictive value would prevent Kudo I and, probably, Kudo II biopsies in the left colon, reducing procedure time and avoiding complications.

Introduction
Patients with longstanding inflammatory bowel disease (IBD), extensive or left ulcerative colitis, or more than one-third colonic-extension Crohn’s disease (CD), have an increased risk for colorectal cancer (CRC) [1,2], and surveillance colonoscopy is recommended to detect dysplasia. Stenosis or previous dysplastic lesions, extensive ulcerative colitis with severe activity, pseudopolyps, first-degree CRC diagnosed before age 50 years,
and primary sclerosing cholangitis are the most important risk factors for CRC [3]. No randomized clinical trials have analyzed if surveillance is effective in this scenario, although some case series suggest such a possibility, like those included in a 2003 review [4], in which the 5-year survival of cancer diagnosed within surveillance was significantly higher than that diagnosed outside surveillance. However, as a recent Cochrane review indicates [5], although there is no clear evidence regarding improved survival, diagnosis of CRC at an earlier stage has a better prognosis.

The SCENIC consensus [6] reinforces the place of chromoendoscopy as the preferred technique for surveillance of dysplasia in IBD patients, including a meta-analysis which concluded that chromoendoscopy detected a significantly greater proportion of patients with dysplasia (relative risk 1.8; 95% confidence interval [CI 1.2–2.6]), with an absolute increase of 6% (95% CI 3–9%) more patients. Thus, evidence regarding chromoendoscopy in this scenario is clear but implementation of chromoendoscopy in different hospitals is challenging, mostly because of the need for systematic training, partnered learning in describing morphology and Kudo pit-pattern, and increased time for the procedure.

Chromoendoscopy involves application of dye to the colonic mucosa to highlight the architecture pooling of dye in the grooves between the colonic crypts and within the colonic pits and polyp ridges. The widely accepted Kudo pit pattern classification [7] is used to differentiate five types of staining patterns to predict neoplastic lesions with high percentages of sensitivity, specificity, and positive and negative predictive values. A recent Spanish real-life study [8] reported a high accuracy with optical diagnosis using the Kudo pit pattern to improve management of these lesions. Our study aimed to analyze results of a chromoendoscopy screening program in seven hospitals in Spain and to assess the possibility of identifying low-risk dysplastic lesions by their endoscopic appearance to avoid histological analysis. We also sought to identify factors associated with dysplasia development.

Materials and methods
We retrospectively collected consecutive screening colonoscopies via chromoendoscopy performed between February 2011 and June 2017 for patients with longstanding IBD in seven different Spanish hospitals. Inclusion criteria were as follows: left or extensive ulcerative colitis and CD involving more than one-third of the colonic mucosa, more than 8 years’ disease duration, and clinical remission (partial Mayo score less than 3 for ulcerative colitis or Harvey Bradshaw < 5 for CRC). Patients had signed informant consent allowing the use of their clinical information for research purposes.

We included demographic characteristics of patients such as sex and age and clinical disease characteristics such as years of disease duration and colonic extension in our database.

Following the Boston Bowel Preparation Scale [9], each endoscopists graded the quality of bowel cleansing. Adequate preparation was defined as a total score ≥6 with no segments <2, excluding procedures with inadequate quality. Based on the Mayo Endoscopy Subscore for ulcerative colitis [10] and Simplified Endoscopic activity Score for CD (SES-CD) [11], the endoscopists recorded endoscopic disease activity, excluding patients with moderate or severe endoscopic activity (Mayo >2 or SES-CD >5).

The chromoendoscopy procedure was performed with indigo carmine (0.2–0.4%) or methylene blue managed with a catheter spray and high-definition endoscopes, including both tertiary referral centers and local community hospitals, according to the SURFACE guidelines [12] and recording the time for the whole procedure. All the endoscopists started to perform chromoendoscopy after systematic training regarding a standardized operating procedure and partner learning as recommended [13]. In all the hospitals, high-definition endoscopes were used with digital magnification but without optical magnification (Olympus Evis Exera II Cv-180 and Evis Exera III Cv-190).

During chromoendoscopy, mucosal healing was described according to each colonic segment and presence or absence of pseudopolyps. Macroscopic characterization of the lesions was based on size and location, Kudo pit pattern, and morphologic characteristics according to the SCENIC consensus-modified Paris classification, excising all visible lesions with biopsy forceps or taking samples of perilesional mucosa with a polypectomy snare to rule out surrounding dysplasia.

Histology was used as the gold standard processing sample, using standard methods. Histologic evaluations were performed by expert gastrointestinal pathologists. If dysplasia was noted, a second pathologist validated the result. Neoplastic lesions were classified according to the Vienna classification into low-grade dysplasia (LGD), high-grade dysplasia (HGD), or CRC.

Statistical analysis was performed using SPSS V.20.0 (IBM, Somers, New York, United States). Quantitative variables are expressed as means and SDs. Categorical variables are expressed as total number and frequencies (%). Quantitative variables were analyzed using the Student’s t-test, and qualitative variables were analyzed using the χ2 test. Univariate binary logistic regression was performed to select variables associated with presence of dysplasia. For multivariable logistic regression analyses, only candidate variables with P values ≤0.05 on univariate analysis were included in the final multivariate model. We included odds ratios (ORs) with 95% CIs to quantify the magnitude of the association. Diagnosis accuracy and CIs for all features were derived from 2×2 tables. Outcome parameters were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy.

Results
During the inclusion period, 719 chromoendoscopies were performed though 10 (1.3%) were excluded due to severe endoscopic activity (1.3%) despite patients being clinically in remission. We finally included 709 consecutive chromoendoscopies (569 patients, 45.7% women) for screening for CRC in a population with longstanding IBD. None of the patients had previous dysplastic lesion or past history of CRC (Fig. 1). Median dura-
tion of disease was 16.7 years (SD 8.1); 80.4% of lesions (n = 458) were ulcerative colitis (46.6% extensive), 17.9% (n = 102) were CD, and 1.6% (n = 9) were indeterminate colitis. Mean duration of colonoscopy was 23.6 ± 19.77 minutes. Despite clinical remission, endoscopic activity was observed in 12.1% of our patients, with a mucosal healing of 87.9% (21.5% Mayo 1 and 66.4% Mayo 2). Adequate bowel preparation based on Boston Bowel Preparation Scale was present in 93.5% of patients. A total of 429 patients underwent only one chromoendoscopy, while 140 patients underwent more than one chromoendoscopy during the study period. Demographic characteristics of the patients are shown in ▶ Table 1.

We identified 2025 lesions (3.56 lesions per patient, 2.86 lesions per chromoendoscopy) and most of them were located proximal to the splenic flexure (76%), including the rectum (16.7%), sigmoid colon (27.7%), or left colon (31.4%); 24% of the lesions were localized in the proximal colon, either in the transverse (10.9%) or right (13.3%) colon. Endoscopic characteristics are shown in ▶ Table 2. Lesions with dysplasia corresponded to 151 different patients, implying that 26.5% of the patients analyzed had dysplastic lesions (1 or more lesion with dysplasia). The number of dysplastic lesions per patient was 0.4.

A total of 1793 (88.5%) lesions were non-neoplastic and histological analysis comprised normal mucosa (43.9%), hyperplastic lesions (36%), inflammatory lesions (13.1%), or other (7%). Two hundred and thirty-two lesions (11.5%) were neoplastic and among these, 223 were LGD (96.1%), 8 were HGD (3.4%), and 1 (0.5%) was CRC (▶ Table 3). Five of the 8 HGD lesions (62.5%) were localized in proximal colon (right or transverse colon) and 75% (6/8) were sessile polyps with a Paris classification of 0-Is or 0-Isp, with just two superficial elevated lesions (Paris Ila). All HGD lesions were completely removed. One invasive CRC was observed in the rectum of a male patient with left ulcerative colitis of 18 years’ duration. This lesion was a depressed 1-cm lesion (Paris 0-IIc), with a Kudo V pit pattern. The patient underwent total colecto-
omy with an ileorectal anastomosis. Concerning non-targeted biopsies, neither perilesional samples nor random samples obtained to assess inflammatory activity showed dysplasia. Dysplastic lesions, compared to non-dysplastic lesions, were more frequently localized in the right colon (OR 2.033; 95% CI 1.225–3.373; P = 0.006) in our univariate and multivariate analysis (Table 4, Table 5). However, lesions localized in the rectum (OR 0.421; 95% CI 0.228–0.779; P = 0.006) or sigmoid colon (OR 0.445; 95% CI 0.255–0.775; P = 0.004) were protective factors for dysplasia. Endoscopic activity during chromoendoscopy was an independent risk factor for dysplasia detection (OR 2.692; 95% CI 1.474–4.916; P = 0.001). Gender, type of IBD (UC/CD), and extension of disease were not associated with dysplastic findings.

Regarding lesion type and size, sessile polyp (Paris 0-Is) (OR 2.751; 95% CI 1.881–4.023; P = 0.000) was a risk factor for dysplastic lesions. Size >1 cm, flat elevated lesions (Paris IIa), flat lesions (Paris IIb), and presence of pseudopolyps were not associated with dysplastic findings.

Taking the Kudo pit pattern as the gold standard for dysplasia detection, endoscopists correctly classified 72/232 neoplastic lesions as Kudo pit pattern ≥III and 1660/1793 non-neoplas-
tic lesions as Kudo pit pattern < III. Thus, sensitivity, specificity, PPV and NPV for dysplasia optical diagnosis were 36 %, 94 %, 41 %, and 92 % respectively. Global accuracy value for onsite optical diagnosis was 87 % (▶ Fig. 2).

To assess the effect of the learning curve on the correlation between Kudo pit pattern and dysplasia detection, we compared the first 50 colonoscopies with the last 50 colonoscopies performed at the most experienced center, and observed a trend towards better accuracy, maintaining the high NPV from the beginning of the study period (▶ Table 7).

### Discussion

Patients with longstanding IBD have a higher risk for CRC, with an incidence of 1.21 per 1000 patient-years in studies published in the last decade [2]. According to a 1992 study [14], guidelines recommended obtaining at least 34 random biopsies from all segments of the colon to detect dysplasia, with a probability of 90 %. Currently, with newer endoscopic technologies, dysplasia is identifiable [15] and most clinical and endoscopic guidelines [3, 16, 17] recommend chromoendoscopy rather than high-definition white-light endoscopy (WLE) or narrow-band imaging for surveillance in IBD longstanding patients with a high evidence level (1B) and a recommendation grade of B. In 2011, a meta-analysis [18] including 1277 patients from six prospective cross-sectional trials showed clear differences in the proportion of dysplastic lesions identified by targeted biopsy between chromoendoscopy and standard WLE. In this meta-analysis, this difference was maintained when we analyzed only flat lesions, with a two to three-fold increase in dysplasia detection per patient and a four- to five-fold increase per lesion. Thus, the difference in yield of dysplasia between chromoendoscopy and WLE was 7 % (95 % CI 3.2 – 11.3) on a per-patient analysis with a number necessary to treat of 14.3. The difference in proportion of lesions detected by targeted biopsies was 44 % (95 % CI 28.6 – 59.1), and flat lesions were 27 % (95 % CI 11.2 – 41.9) in favor of chromoendoscopy. With respect to clinical trials, a Spanish multicenter prospective cohort study...
B. Sicilia et al. Even non-experts identify white light-targeted biopsies. A recently published paper with rate with chromoendoscopy-targeted biopsies compared with [8] demonstrated a considerable increase in dysplasia detection band imaging and chromoendoscopy [19].

any difference in detecting dysplasia when comparing narrow-
sion. Such findings support the conclusions of several articles,
slightly elevated (Paris 0-IIa) or flat (Paris 0-IIb-c) resected le-
nor in polyps (Paris 0-Is/Paris 0Ip) nor in any other type of
IBD, dysplasia not being detected in any perilesional biopsy,
setting, reported a dysplasia detection rate of 11.5 % via targe-
toscopy and detected 27 of 44 dysplastic lesions by chromoen-
doscopy. Gasia et al [21] detected a total of 243 lesions in a co-
hort of 454 IBD patients who underwent surveillance between
2011 and 2014. Moreover, a prospective multicenter trial in
Spain [8] confirmed the value of dye-based chromoendoscopy
in 350 IBD patients undergoing surveillance colonoscopy under
real-life conditions with white-light colonoscopy assessment
followed by indigo carmine chromoendoscopy in a segmental fashion. The results of this last study showed a
57 % incremental yield for IBD-associated neoplasia using dye-
based chromoendoscopy vs white-light colonoscopy, with a
dysplasia rate of 15.7 % (1 CRC, 5 HGD, 88 LGD).

The current study, a multicenter cohort that included 709
Chromoendoscopies of 569 consecutive patients in a real-life setting, reported a dysplasia detection rate of 11.5 % via target-
ted chromoendoscopic biopsies in patients with longstanding
IBD, dysplasia not being detected in any perilesional biopsy,
nor in polyps (Paris 0-Is/Paris 0Ip) nor in any other type of
slightly elevated (Paris 0-IIa) or flat (Paris 0-IIb-c) resected le-
sion. Such findings support the conclusions of several articles,
the most recent one published by Lahiff et al [22], where a low
efficacy was found after analyzing the probability of detecting
dysplasia “polyp-adjacent” biopsies in IBD patients by using
high-definition endoscopes and techniques such as chromoen-
doscopy. Neither did we find dysplasia in random biopsies by
colic segment, despite the fact that the purpose of this study
with random biopsies was to analyze histological healing and
not presence of invisible dysplasia; practice which remains con-
troversial.

Pseudopolyps were present in one-third of our chromoen-
doscopies and contrary to the literature, they were not asso-
ciated with presence of dysplasia. However, and according to
data published to date, lesions localized to the proximal colon
(right or transverse colon) and elevated lesions (Paris 0-Is) are
risk factors for dysplasia [19]. Pseudopolyps were described as
a risk factor for a higher incidence of CRC (OR 2.1), although
other risk factors such as stenosis (OR 5.7) or primary scleros-
ing cholangitis (OR 4.8) demonstrated a higher risk [3]. To
date, without narrow-band imaging or dye use, it is difficult to
differentiate an inflammatory pseudopolyp from a dysplastic
polyp, which could lead to overestimation of CRC risk in the
presence of pseudopolyps. However, pseudopolyps are a con-
sequence of severe colonic inflammation, which is another risk
factor for higher CRC incidence. Thus, results of other studies
that employ chromoendoscopy will be required to confirm our
results.

Degree of inflammation is currently an established risk fac-
tor for CRC. In a cohort of 418 patients with ulcerative colitis
[23] who were followed for a median of 6.7 years and received
an average of 5 surveillance colonoscopies at a median interval
of 0.8 years, 15 patients progressed to advanced neoplasia
(HGD or CRC), while 65 progressed to any neoplasia (LGD,
HGD, or CRC). A significant relationship was found between
the degree of inflammation and progression to advanced neo-
plasia, with a unit increase in the mean inflammation score
associated with a three-fold increase in risk of advanced neopla-
ia. In our study, endoscopic activity during chromoendoscopy
was an independent risk factor for dysplasia detection.

Regarding lesion size and morphology, we identified more
dysplastic findings in Paris 0-Is or 0-Isp lesions. In a 2007
meta-analysis [24], dysplasia progression to CRC was 14 per
1000 person-years (95 % CI: 5.0 – 34) and incidence of any ad-
vanced lesion was 30 per 1000 person-years (95 % CI: 12 – 76).
Other studies on natural history of LGD published since the
2007 review have reported progression rates ranging from
4.9 % to 30 % [25, 26]. When analyzing only polypoid lesions,
this risk seems to be much lower (0.9 %) [27]. Only two studies
describe long-term progression when dysplastic lesions are
identified by chromoendoscopy and reported controversial re-
sults because they employed notably different methodologies
[20, 28]. It will be interesting if the polypoid dysplastic lesions
found in chromoendoscopy in our IBD population have the
same risk for CRC as flat lesions (Paris 0-Ilb) or flat elevated le-
sions (Paris 0-Ila) in the long term. We did not find any other risk
or protective factor for dysplasia with regard to sex, gender,
extensive colitis, or lesion size.
Identification of Kudo pit pattern is challenging in IBD patients and en bloc removal of all lesions is recommended. Moreover, because of chronic inflammation, endoscopic management of dysplasia is associated with a higher rate of complications [29]. Thus, if we were able to correctly identify lesions without dysplasia, we could leave them onsite without endoscopic complications, reducing procedure time. Overall, we reported very low rates of sensitivity and PPV compared with reports from other European groups [30]. However, we had similar and high percentages of specificity and NPV when high-definition endoscopes without optical magnification were used [31], and even with endoscopes with optical magnification where sensitivity percentages are clearly higher without losing high NPV percentages [32]. This means that during endoscopy, when the endoscopist describes a lesion with a high probability of dysplasia (Kudo > III), probability of correlation with histological findings is low since many lesions do not have dysplasia. However, when a lesion with low probability of dysplasia (Kudo I or II) is described, probability of correlation with histological findings is very high. In a screening technique, it is important to correctly identify disease (in this case, dysplastic lesions), and high NPV indicates that these techniques are valuable for exclusion of dysplasia.

It is also important to ascertain if training affects outcomes because most of the existing chromoendoscopic data, especially data demonstrating positive results, come from centers where gastroenterologists have particular expertise in chromoendoscopy. Although Mooiweer et al [33] concluded that a lower neoplasia detection rate could be due to endoscopist inexperience, Carvallal et al [8] reported no statistical differences in dysplasia detection when comparing expert (> 20 chromoendoscopies) and non-expert endoscopists. In our study, all the endoscopists commenced performing chromoendoscopy after systematic training, standardization of the operative procedure, and partnered learning. However, not all the endoscopists were experts as, with time, they learned by performing their own chromoendoscopies at their hospitals. We compared the first 50 chromoendoscopies with the last 50 chromoendoscopies at the center with the most experience (more than 20 chromoendoscopies done previously) and observed that the NPV remained high, while the PPV improved. Thus, the endoscopists were able to detect non-neoplastic lesions from the outset, improving the correlation between Kudo III and dysplastic lesions with experience.

According to these results, this high NPV and left colon location could prevent removal of all identified lesions, at least, in the sigmoid colon and rectum because of the very low probability of dysplasia, with regard to Kudo I or II pit pattern. These results are important for two reasons. First, if low-probability dysplastic lesions are not removed, procedure duration, which is a major problem with chromoendoscopy, will decrease. Second, in asymptomatic patients, large and numerous Kudo I or II pit pattern lesions are observed, mostly in the sigmoid colon and rectum. If these are removed, complications such as bleeding or even perforation may occur, even when some of these lesions may eventually be found to be non-dysplastic. Nevertheless, Kudo pit pattern II lesions could have a different meaning because most of them correspond to hyperplastic lesions in histology, and could be serrated lesions, which have a potential for neoplasia.

Conclusion

In conclusion, our results confirmed the efficacy of chromoendoscopy for dysplasia detection, with a dysplasia yield of 11.5%, in a real-life screening study. Although in our study, the Kudo pit pattern was not an accurate diagnostic method for predicting dysplastic lesions, the high NPV and the protective influence of left colonic lesions for dysplastic findings could prevent removal of lesions with Kudo pit pattern I and, perhaps, Kudo pit pattern II in the rectum or sigmoid colon because they have a markedly low probability of dysplasia; thus, improving procedure time and avoiding endoscopic complications.

STROBE guidelines were used for elaboration of this article, using the checklist of each one of the points of the methodology specified to guarantee the best communication of this observational study [34].

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Competing interests

None

References