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Adherence to endoscopic surveillance for advanced lesions and colorectal cancer in inflammatory bowel disease: an AEG and GETECCU collaborative cohort study

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The members of the Young Group of AEG and GETECCU that also participated in the study are listed in Appendix 1.

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Summary

Background and Aims: Patients with colonic inflammatory bowel disease (IBD) have a high risk of colorectal cancer (CRC). Current guidelines recommend endoscopic surveillance, yet epidemiological studies show poor compliance. The aims of our study were to analyse adherence to endoscopic surveillance, its impact on advanced colorectal lesions, and risk factors of non-adherence.

Methods: A retrospective multicentre study of IBD patients with criteria for CRC surveillance, diagnosed between 2005 and 2008 and followed up to 2020, was performed. Following European guidelines, patients were stratified into risk groups and adherence was considered when surveillance was performed according to the recommendations (±1 year). Cox-proportional regression analyses were used to compare the risk of lesions. *p*-values below 0.05 were considered significant.

Results: A total of 1031 patients (732 ulcerative colitis, 259 Crohn's disease and 40 indeterminate colitis; mean age of 36 ± 15 years) were recruited from 25 Spanish centres. Endoscopic screening was performed in 86% of cases. Adherence to guidelines was 27% (95% confidence interval, CI = 24–29). Advanced lesions and CRC were detected in 38 (4%) and 7 (0.7%) patients respectively. Adherence was associated with increased detection of advanced lesions (HR = 3.59; 95% CI = 1.3–10.1; $p = 0.016$). Risk of delay or non-performance of endoscopic follow-up was higher as risk groups increased (OR = 3.524; 95% CI = 2.462–5.044; $p < 0.001$ and OR = 4.291; 95%CI = 2.409–7.644; $p < 0.001$ for intermediate- and high- vs low-risk groups).

Conclusions: Adherence to endoscopic surveillance allows earlier detection of advanced lesions but is low. Groups at higher risk of CRC are associated with lower adherence.

1 | INTRODUCTION

Inflammatory bowel disease (IBD) is associated with an altered immune response in genetically pre-disposed subjects.[1,2] Due to the inherent chronic mucosal inflammation, patients with colonic IBD have a twofold higher risk of colorectal cancer (CRC) than the general population.[3] IBD CRC typically appears at an early age, in proximal locations, with a higher frequency of multiple and poorly differentiated lesions, representing a greater diagnostic challenge.[4–6]

Several factors increase the risk of CRC, some related to IBD specifically, such as early age at diagnosis, longer disease duration, extent and severity of inflammation, presence of pseudopolyps or stenosis or coexistence of primary sclerosing cholangitis (PSC); and some found in the general population including smoking habit or CRC family history.[7,8]

Endoscopic surveillance has been associated with reduced risk of advanced and interval neoplasia as well as the reduction in mortality from CRC in observational studies.[9–11] Accordingly, several clinical guidelines have been developed for endoscopic surveillance of malignant or premalignant lesions in IBD.[12–21] Nevertheless, only a few epidemiological studies have evaluated compliance with early

Study highlights

What is known

- Patients with colonic inflammatory bowel disease have a higher risk of colorectal cancer than the general population.
- Endoscopic surveillance is associated with a reduced risk of advanced and interval neoplasia.

What is new here

- Adherence to endoscopic surveillance guidelines is low in Spain.
- Adherence to endoscopic surveillance recommendations is associated with higher and earlier detection of premalignant colorectal lesions.
- Higher risks groups are correlated with poorer adherence to endoscopic recommendations.

detection programmes, showing poor adherence even in patients at high risk of CRC.[22–25]

Given the lack of data in our setting, in agreement with previous studies, we hypothesised that adherence to clinical guidelines is low in Spain. The aims of our study were to evaluate: (i) adherence to endoscopic surveillance recommendations, (ii) impact of non-adherence on advanced lesions or CRC detection rate and (iii) risk factors associated with non-adherence.

2 | MATERIALS AND METHODS

2.1 | Study design and patient selection

A longitudinal, retrospective and multicentre cohort study was performed. All IBD patients diagnosed between 2005 and 2008 and followed up in any participating centre between 2005 and 2020 were screened for eligibility. Inclusion criteria were patients with left-sided or extensive ulcerative colitis (UC) both at diagnosis and who experienced progression from proctitis during the disease course, Crohn's disease (CD) involving more than one-third of the colon or indeterminate colitis according to standard criteria, with the clinical course of at least 8 years since symptoms onset or with PSC regardless of disease extent or duration.[26,27] Patients with CRC before IBD diagnosis or with reservoir and ileoanal anastomosis without dysplasia or CRC history were excluded.

The study was promoted by two Spanish national associations (AEG and GETECCU). The study design and variables to be included were discussed with all study collaborators and a well-defined protocol was sent to all participating centres prior to data collection. A national electronic database (REDCap—Research Electronic Data Capture) was created for data collection and management. Demographic and clinical data, inclusion and/or follow-up in the endoscopic surveillance programme, time of inclusion, time of follow-up colonoscopies, reasons for non-surveillance, degree of cleansing based on the Boston scale,[28] endoscopic and histological inflammatory activity, diagnostic techniques used (white light or chromoendoscopy including any dye-based or virtual), advanced lesions or CRC detection rate, lesions characteristics and applied treatments (endoscopic or surgical, en bloc or fragmented resection) were recorded. European Crohn's and Colitis Organisation (ECCO) guidelines were chosen to evaluate adherence as the most widely used ones in our environment.[20,21]

2.2 | Definitions

Endoscopic surveillance programme inclusion was defined when a first colonoscopy was performed to detect malignant or pre-malignant lesions. Surveillance follow-up was defined by subsequent colonoscopies performed with the same intention.

Adherence to endoscopic inclusion was defined when first colonoscopy was performed within 8 ± 1 years after symptoms onset or immediately after PSC diagnosis. Adherence to ongoing surveillance was defined when follow-up colonoscopies were performed within the appropriate time interval ± 1 year based on risk stratification. Patients with high-risk features (stricture or dysplasia within the past 5 years, PSC, extensive colitis with severe inflammation, a family history of CRC in a first-degree relative diagnosed before age 50 years) should had their next endoscopy approximately at 1 year. Patients with intermediate-risk factors (extensive colitis with mild or moderate inflammation, post-inflammatory polyps or a family history of CRC in a first-degree relative diagnosed at age 50 years and above) should had their next endoscopy scheduled for 2–3 years. Patients with neither intermediate- nor high-risk features should had their next surveillance colonoscopy scheduled at 5 years follow-up. Adherence to the surveillance recommendations was considered when both inclusion and follow-up recommendations were met. The absence of surveillance colonoscopies when indicated during the study period or its performance before (in advance) or after (delayed) 1 year of the required time, were considered non-adherence.

Adenomatous lesions with >25% villous component, >1 cm or with high-grade dysplasia or serrated lesions >1 cm or with any degree of dysplasia were considered advanced lesions.

2.3 | Statistical analysis

The software used for all analysis was spss version 27.

Differences in adherence to surveillance recommendations were compared using Student's *t*-test while normality assumptions held true; otherwise, Mann–Whitney test was used for continuous data and the chi-squared or Fisher test for categorical data, as required. Measures of association between qualitative variables were reported as odds ratio (OR) with 95% confidence intervals (95%CI) and *p* values.

Time to advanced lesions and/or CRC detection was performed through Kaplan–Meier and Log-rank test. Cox regression analyses were used to analyse the independent contribution of each variable to time-to-event. Multivariable Cox regression was used to study the effect of adherence and other significant and relevant variables from the univariable analyses on time to advanced lesions and/or CRC. Results were presented as estimated hazard ratios (HR) with respective 95%CI and *p* values.

All tests were two-sided and a $p < 0.05$ was considered statistically significant.

2.4 | Ethical statement

The study was approved by the Hospital Clínico Universitario de Valencia Institutional Review Boards in April 2020 (2020/004). The Ethics Committees of all participating hospitals reviewed and approved the study protocol. This study complies with the principles of Good Clinical Practice and the Helsinki Declaration.

3 | RESULTS

3.1 | Patients characteristics

A total of 1031 (732 UC, 259 CD and 40 indeterminate colitis) patients were recruited from 25 Spanish centres (Table 1; Figure 1). Of the participating hospitals, 17 (68%) were tertiary and 8 (32%) regional. Almost all of them (92%) had a specialised IBD Unit, which was accredited to quality standards of the Spanish Working Group on CD and UC (GETECCU) in 60% of cases. Only two hospitals (8%) lacked a general population CRC screening programme. A total of nine (36%) and 11 (44%) hospitals had a specific room or a specialised endoscopist for IBD patients respectively. Patient distribution by hospital characteristics is summarised in Table 2.

Of all patients, 888 (86%) were included in the endoscopic surveillance programme (82% of CD, 87% of UC and 93% of indeterminate colitis patients). Mean time from IBD or PSC diagnosis to first screening colonoscopy was 8.4 ± 2.4 and 1 ± 2.8 years, respectively. Median follow-up of patients after index colonoscopy was 4 (interquartile range -IQR-: 3–6) years. According to patient characteristics and results of the first colonoscopy, 62 (7%), 250 (28%) and 576 (65%) patients were classified into high-, intermediate- and low-risk groups, respectively, to schedule ongoing surveillance. A total of 478 (54%) of included patients underwent endoscopic follow-up. According to risk stratification, 76%, 68% and 44% of patients in the high-, intermediate- and low-risk groups had a subsequent screening with a mean time from inclusion to first follow-up colonoscopy of 1.9 ± 1.5, 2.9 ± 1.7 and 3.7 ± 1.6 years respectively. Up to 67% of patients underwent the required number of follow-up colonoscopies, while 27% and 6% underwent at least one fewer or more than required by ECCO guidelines. Reasons for non-inclusion or follow-up in the surveillance programme are described in Figure 1. Losses to follow-up were included among other reasons for not performing endoscopic surveillance. Characteristics of the procedures are summarised in Table 3.

TABLE 1 Demographic and clinical characteristics of study population in the total cohort and in adherence and non-adherence groups

Variable	Results			
	Total ($N = 1031$)	Adherence ($n = 274$)	Non-adherence ($n = 757$)	*p*-value
Male	536 (52)	138 (51)	396 (53)	0.581
Smoking habit	427 (41)	123 (46)	304 (41)	0.173
Family history of CRC	45 (5)	10 (4)	35 (5)	0.499
PSC	27 (3)	6 (2)	21 (3)	0.604
Age at IBD diagnosis (years)	36 (15)	39 (15)	36 (15)	0.014
IBD type				
UC	732 (71)	208 (76)	524 (69)	0.088
CD	259 (25)	59 (22)	200 (26)	
Indeterminate	40 (4)	7 (3)	33 (4)	
CD location				
Ileal	5 (2)	1 (1)	4 (3)	0.989
Colonic	83 (32)	19 (32)	64 (32)	
Ileocolonic	171 (66)	39 (66)	132 (66)	
Upper disease[a]	11 (4)	1 (2)	10 (5)	
CD behaviour				
Inflammatory	199 (77)	51 (86)	148 (74)	0.098
Stricturing	25 (9)	2 (3)	23 (12)	
Penetrating	35 (14)	6 (10)	29 (15)	
UC extent				
Proctitis	14 (2)	3 (2)	11 (2)	0.144
Left-side colitis	348 (48)	88 (42)	260 (50)	
Extensive colitis	370 (50)	117 (56)	253 (48)	

Note: Continuous variables are presented as mean with standard deviation, categorical variables are presented as absolute and relative frequencies (%). Comparisons were performed using t-test for continuous and Chi-Square for categorical data.

Abbreviations: CRC, Colorectal cancer; PSC, primary sclerosing cholangitis; IBD, Inflammatory Bowel Disease; UC, Ulcerative colitis; CD, Crohn's disease.

[a]L4 was a modifier added to L1-L3 when concomitant upper disease was present.

FIGURE 1 Flow chart of study cohort. IBD, inflammatory bowel disease

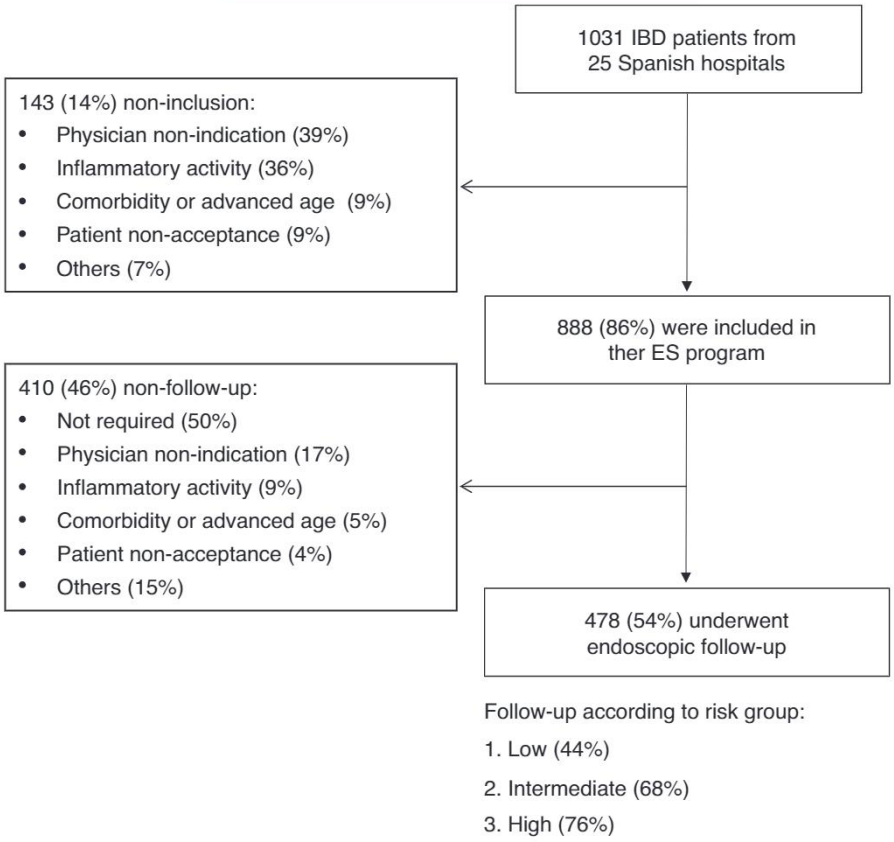


TABLE 2 Distribution of patients according to hospital characteristics in the total cohort and in adherence and non-adherence groups

Variable	Results			
	Total (*N* = 1031)	Adherence (*n* = 274)	Non-adherence (*n* = 757)	*p*-value
Hospital type				
Tertiary	234 (23)	217 (79)	580 (77)	0.383
Regional	797 (77)	57 (21)	177 (23)	
Specialised IBD Unit	1004 (97)	269 (98)	735 (97)	0.337
Accredited IBD Unit	796 (77)	215 (79)	581 (77)	0.562
Number of IBD consultations per year				
<500	42 (4)	8 (3)	34 (5)	0.488
500-1500	288 (28)	80 (29)	208 (28)	
>1500	701 (68)	186 (68)	515 (68)	
Number of IBD endoscopies per year				
<400	393 (38)	93 (34)	300 (40)	0.003
400–800	239 (23)	49 (18)	190 (25)	
>800	399 (39)	132 (48)	267 (35)	
Population CRC screening programme	990 (96)	257 (94)	733 (97)	0.028
Specific IBD endoscopy room	311 (30)	88 (32)	223 (30)	0.411
Specialised endoscopist	426 (41)	115 (42)	311 (41)	0.798

Note: Variables are presented as absolute and relative frequencies (%). Comparisons were performed using chi-Squared test.

Abbreviations: CRC, colorectal cancer; IBD, inflammatory bowel disease.

3.2 | Adherence to endoscopic surveillance guidelines

Adherence to first or subsequent surveillance colonoscopies was 43% (95%CI = 40–46) and 57% (95%CI = 54–60), respectively, with a total adherence rate of 27% (95%CI = 24–29). Mean time from IBD or PSC diagnosis to first colonoscopy was 8.6 ± 2.8 vs 8 ± 1.1 ($p < 0.001$) and 1.3 ± 3 vs 0.2 ± 0.4 years ($p = 0.154$) in non-adherence and adherence groups respectively. Adherence to follow-up according to risk stratification was 68%, 55% and 61% in low-, intermediate- and high-risk groups respectively ($p = 0.001$). Mean time from inclusion to first follow-up colonoscopy was 4.6 ± 0.8 vs 2.6 ± 1.6 ($p < 0.001$), 2.9 ± 0.9 vs 3 ± 3.2 ($p = 0.838$) and 1.4 ± 1.1 vs 3.6 ± 1 years ($p < 0.001$) in adherence and non-adherence patients from the low-, intermediate- and high-risk groups respectively. Reasons for non-adherence are represented in Figure 2.

TABLE 3 Characteristics of surveillance colonoscopies

Variable	Results	
	First procedure ($n = 888$)	Follow-up ($n = 478$)
Repeated colonoscopy	55 (6)	29 (6)
Poor preparation	37 (4)	18 (4)
Inflammatory activity	13 (2)	11 (2)
Procedural complications	5 (1)	0 (0)
Complete visualisation of the colon	840 (95)	448 (94)
Detection technique		
White light	667 (75)	295 (62)
Chromoendoscopy	221 (25)	183 (38)
Biopsy protocol		
Random	493 (56)	227 (47)
Targeted	177 (20)	97 (20)
No biopsies	218 (24)	154 (32)
Cleaning scale		
Boston ≥6	840 (95)	445 (93)
Boston <6	48 (5)	33 (7)
Inflammatory activity	270 (31)	166 (35)
Mild	159 (18)	121 (25)
Moderate	101 (11)	41 (9)
Severe	10 (1)	4 (1)
Endoscopic lesions		
Visible	207 (23)	105 (22)
Invisible	9 (1)	6 (1)

Note: Variables are presented as absolute and relative frequencies (%).

3.3 | Detection of advanced colorectal lesions or CRC

Advanced lesions and CRC were detected in 38 (4%) and 7 (0.7%) patients during endoscopic surveillance procedures respectively. The median number of advanced lesions per patient and per colonoscopy was 1 (IQR 1–1.5) and 1 (IQR 0.5–1). Mean time from IBD diagnosis to detection of advanced lesions was 9.3 ± 3 years. Twenty-nine (76%) of the advanced lesions were adenomas while 9 (24%) were serrated polyps, with a median size of 13 (IQR 10–15) mm. High-grade dysplasia was present in eight (24%) cases, with only three (8%) lesions reviewed by two pathologists. Almost all lesions (92%) were endoscopically resected, mainly (74%) with en-block resection. Cumulative probability of advanced lesions in our cohort was 0.4%, 2.2% and 3.9% at 5, 10 and 15 years after IBD diagnosis. Only one CRC was detected in the first screening colonoscopy, while the other six cases were diagnosed in subsequent procedures with a mean time from IBD diagnosis until CRC detection of 11.9 ± 2 years. Four (0.4%) more cases of CRC were diagnosed in endoscopic procedures performed for other reasons with a mean time from IBD diagnosis until CRC detection of 5.8 ± 4 years. Risk of CRC in patients without surveillance was 1.4% (95%CI = 0.5–3.4%). The total cumulative probability of CRC in our cohort was 0.3%, 0.6% and 1.6% at 5, 10 and 15 years of follow-up.

3.4 | Factors associated with advanced colorectal lesions or CRC

Significant relationships were observed between endoscopic follow-up and advanced lesions (7.3% vs 1.8%; HR = 6.2; $p = 0.013$) or CRC diagnosis (1.9% vs 0.4%; HR = 4.9; $p = 0.027$). None of the seven CRC cases detected in patients with endoscopic surveillance had spread to other parts of the body (T1-T3, N0, M0), while lymphatic involvement or metastasis was observed in patients without endoscopic follow-up (T3-T4, N1, M1).

Total adherence was not significantly associated with advanced lesions (HR = 1.5; 95%CI = 0.8–2.9; $p = 0.259$) or CRC diagnosis (HR = 1.1; 95%CI = 0.3–4; $p = 0.926$). When lack of adherence was only considered if there was either a delay or non-performance of endoscopic surveillance, adherence to follow-up recommendations was associated with higher detection of advanced lesions (HR = 3.6; 95%CI = 1.3–10.1; $p = 0.010$) (Figure 3), but not with CRC (HR = 1.1; 95%CI = 0.3–4.1; $p = 0.898$).

Other risk factors for advanced lesions and CRC are summarised in Tables 4 and 5. In the multivariable Cox-regression analyses including adherence to follow-up recommendations and other clinical risk factors, age at IBD diagnosis, stratified risk group and adherence remained as independent predictors of advanced lesions (Table 4). Older age at IBD diagnosis and PSC were associated with a higher CRC detection rate (Table 5). Among the techniques used, chromoendoscopy (HR = 2.2; 95%CI = 1.1–4.2; $p = 0.022$) and targeted biopsies (HR = 4.6; 95%CI = 2.4–8.7; $p < 0.001$) were associated with

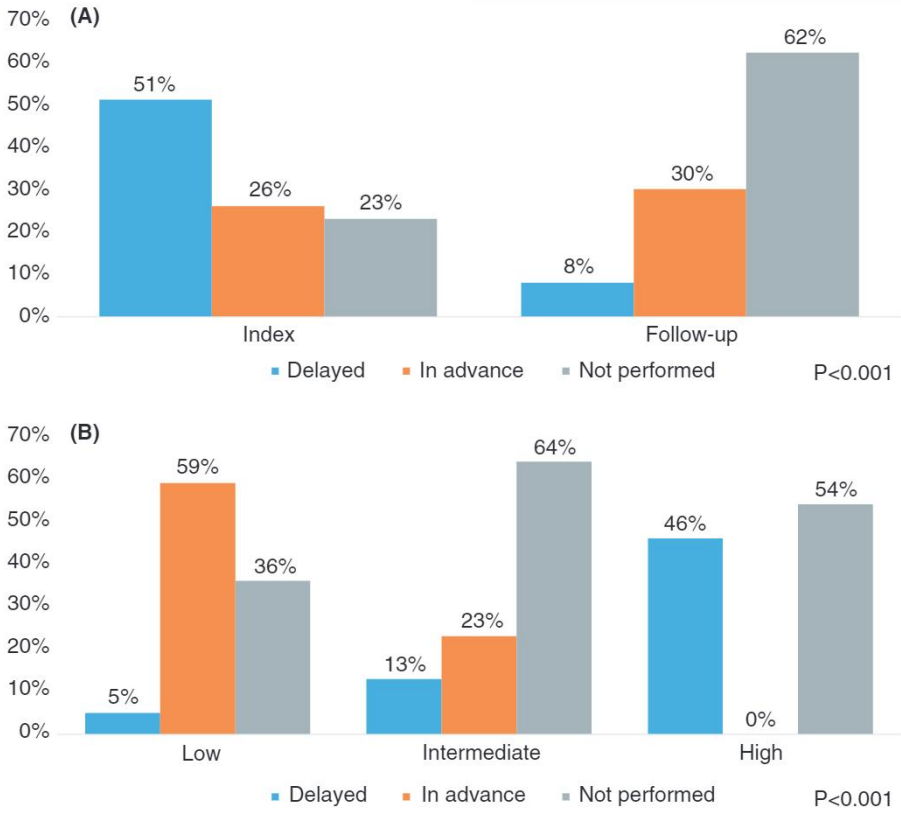
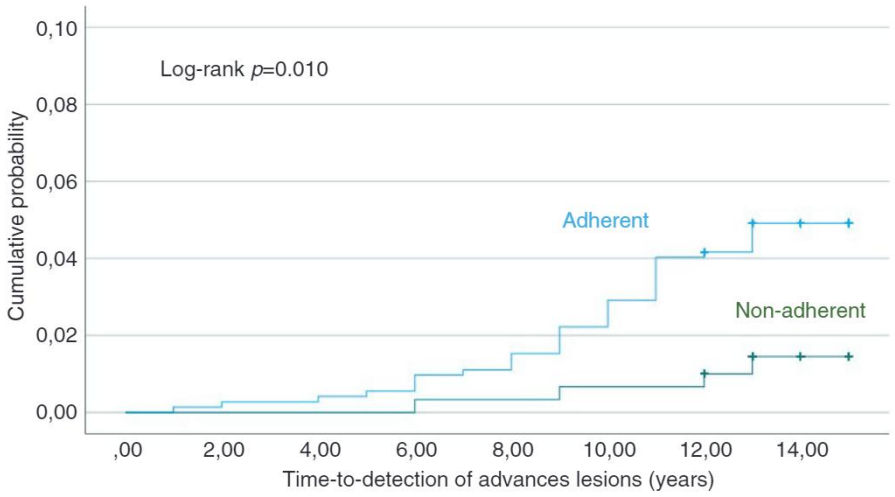


FIGURE 2 Reasons for non-adherence to endoscopic surveillance according to the procedure (A) and stratified risk group (B)

FIGURE 3 Relationship between adherence and time-to-detection of advanced colorectal lesions: Kaplan-Meier



a higher diagnosis of advanced lesions. In a time analyses, both chromoendoscopy (40% vs 16%; OR = 3.5; 95%CI = 2.5–4.7; $p < 0.001$) and targeted biopsies (26% vs 16%; OR = 1.8; 95%CI = 1.3–2.6; $p < 0.001$) were more often used in those procedures performed after 2017.

3.5 | Risk factors of non-adherence

Risk factors of non-adherence are summarised in Tables 1 and 2. Thirteen percent, 34% and 39% non-adherence in the form of non-performance or delay of follow-up procedures was observed in low-, intermediate- and high-risk groups, respectively ($p < 0.001$), with a higher risk of delay or non-performance of endoscopic follow-up as risk groups increased (OR = 3.5; 95%CI = 2.5–5.04; $p < 0.001$ and OR = 4.3; 95%CI = 2.4–7.6; $p < 0.001$ for intermediate- and high- vs low-risk groups). UC was associated with a higher adherence rate (28% vs 22% in non-UC; OR = 1.4; 95%CI = 1.02–1.9; $p = 0.036$), while CD was associated with non-performance or delay in follow-up procedures (36% vs 27% in non-CD; OR = 0.7; 95%CI = 0.5–0.9; $p = 0.013$). A higher adherence rate was shown in patients diagnosed with IBD at an older age (OR = 1.01; 95%CI = 1.002–1.02; $p = 0.014$).

TABLE 4 Demographic and clinical risk factors of advanced lesions

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Male/Female	1.8	0.9–3.5	0.093			
Smoking habit	1.2	0.6–2.2	0.640			
Family history of CRC	1.9	0.6–6.2	0.292			
PSC	1.02	0.1–7.5	0.983			
Age at IBD diagnosis (yr)	1.1	1.03–1.1	<0.001	1.1	1.03–1.1	<0.001
IBD type						
CD	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
UC	6.3	1.5–26.2	0.011	3.9	0.9–16.4	0.063
Indeterminate	3.3	0.3–35.9	0.335	2.1	0.2–23.3	0.549
CD location						
Ileal	Ref.	Ref.	Ref.			
Colonic	1.0	0.0–6096	1.000			
Ileocolonic	39.1	0.0–5358	0.888			
CD behaviour						
Inflammatory	Ref.	Ref.	Ref.			
Stricturing	0.03	0.0–8415	0.758			
Penetrating	0.03	0.0–2985	0.715			
UC extent						
Proctitis	Ref.	Ref.	Ref.			
Left-side colitis	0.5	0.1–3.8	0.503			
Extensive colitis	0.9	0.1–6.4	0.881			
Risk group						
Low	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Intermediate	2.2	1.1–4.6	0.032	2.2	1.1–4.6	0.032
High	6.2	2.7–14.2	<0.001	6.2	2.7–14.4	<0.001
Adherence (vs delay or non-performance of endoscopic surveillance)	3.6	1.3–10.1	0.016	3.3	1.1–9.3	0.028

Note: Analyses were performed using Cox-regression univariable and multivariable test.
Abbreviations: CD, Crohn's disease; CRC, colorectal cancer; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; ref, reference; UC, ulcerative colitis.

4 | DISCUSSION

This longitudinal, multicentre cohort study addresses the issue of adherence to endoscopic surveillance recommendations for IBD in Spain and assesses its real impact on clinical practice.

The prevalence of IBD continues to raise in western countries, with a rapidly increasing incidence in industrialising countries.[29,30] Although CRC risk among patients with IBD appears to be declining in recent years,[31,32] it remains higher than in the general population, with poorer overall survival than in non-IBD CRC patients.[6] Adequate control of mucosal inflammation and endoscopic surveillance programmes are essential to reduce incidence.[9–11] While controlling mucosal inflammation is intrinsic to disease management and both patients and doctors aim to achieve this as soon as possible, surveillance recommendations are in many cases not a priority, despite the long-term impact this can have. A retrospective study by Velayos FS et al. reported that only 25% of 771 patients with UC for more than 8 years underwent follow-up colonoscopy over a 2-year period, reaching 39% in PSC-associated cases.[22] A survey of 244 Dutch gastroenterologists showed that 95% performed endoscopic follow-up of UC patients and 65% of CD patients; however, only 27% followed international clinical practice guidelines.[23] Similarly, a recent retrospective cohort study conducted in 116 UC patients showed that almost half of them had a first screening colonoscopy more than 10 years after diagnosis.[25]

In line with previous studies, our results showed that 86% of patients with criteria for CRC screening underwent surveillance colonoscopy. However, compliance with ECCO guidelines was observed in only 27% of cases. This percentage seems suboptimal considering the 45% minimum and 65% desirable participation thresholds in European guidelines for quality assurance in CRC screening and diagnosis.[33] Nevertheless, these targets for adherence to screening

TABLE 5 Demographic and clinical risk factors of CRC

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Male/Female	1.1	0.3–3.5	0.899			
Smoking habit	1.3	0.4–4.6	0.646			
Family history of CRC	2.3	0.3–18.1	0.431			
PSC	13.9	3.7–52	<0.001	7.4	1.2–47.6	0.034
Age at IBD diagnosis (year)	1.1	1.02–1.1	0.003	1.1	1.02–1.1	0.007
IBD type						
CD	Ref.	Ref.	Ref.			
UC	34.8	0.1–12747	0.238			
Indeterminate	0.9	0.0–640015	1.000			
CD location						
Ileal	–	–	–			
Colonic						
Ileocolonic						
CD behaviour						
Inflammatory	–	–	–			
Stricturing						
Penetrating						
UC extent						
Proctitis	Ref.	Ref.	Ref.			
Left-side colitis	1900	0.0–7242	0.951			
Extensive colitis	4716	0.0–1795	0.945			
Risk group						
Low	Ref.	Ref.	–	Ref.	Ref.	–
Intermediate	0.8	0.1–7.4	0.817	0.6	0.1–5.8	0.656
High	16.6	3.9–69.4	<0.001	5.4	0.9–31.4	0.059
Adherence (vs delay or non-performance of endoscopic surveillance)	1.1	0.3–4.1	0.898			

Note: Analyses were performed using Cox-regression univariable and multivariable test. No cases were available for analyses in CD location or behaviour.

Abbreviations: CD, Crohn's disease; CRC, colorectal cancer; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; ref, reference; UC, Ulcerative colitis.

recommendations in the general population can hardly be applied in IBD cases. In fact, in most patients in whom ECCO recommendations were not followed, endoscopic surveillance was carried out, but over a different time interval than was indicated by guidelines. Of the 14% of patients not undergoing a first screening colonoscopy, in over a third of cases this was because the physician did not order the procedure, highlighting an area for improvement. Other factors, however, such as inflammatory activity or preferences of patients who are already receiving multiple colonoscopies due to their primary disease, all play an important role and may be more difficult to control.

Another limitation when insisting on compliance with surveillance recommendations is the lack of demonstrated efficacy of the colonoscopy screening programme in clinical trials, as evidence comes from observational studies.[9-11] Our results reinforce that performing follow-up colonoscopy increases by five to six times the probability of finding pre-malignant lesions or early-stage cancer and, therefore, seems of crucial importance. However, one-third of CRC cases in our study were detected before endoscopic surveillance was indicated. Given that CRC probability at 5 years of IBD diagnosis was 0.2%, an earlier screening programme in all IBD patients may be difficult to justify from a cost-effectiveness standpoint. Nevertheless, performing a screening colonoscopy after remission to confirm the absence of dysplasia before applying the current surveillance guidelines could be a suitable approach as many cases of CRC are missed lesions of the index colonoscopy.[34]

Compliance with guidelines recommendations was associated with greater detection of advanced colorectal lesions, which would

allow earlier treatment of pre-malignant lesions and, ultimately, avoid the development of CRC. This idea supports previous results reported by a single tertiary centre in which a high adherence rate was associated with a high adenoma and low dysplasia or CRC detection.[35]

Risk factors of advanced lesions or CRC, such as older age or PSC, were consistent with previous data.[7,8] As expected, risk stratification was also associated with both risk and time to detection of colorectal lesions. However, non-adherence in the form of non-performance or delay of follow-up procedures was higher as risk group increased. Whereas low-risk patients had their first follow-up surveillance colonoscopy at 3.7 years from the first one, high-risk patients underwent follow-up colonoscopy 2 years after the previous one probably because both patients and physicians tend to delay repeat procedures. As we have seen, this may have negative consequences and, therefore, greater attention should be paid to surveillance recommendations, especially in patients with high-risk factors.

Precursor lesions of CRC in IBD are usually flat or non-visible dysplastic foci. Chromoendoscopy with targeted biopsies is more effective and cost-efficient than white light with random biopsies, making it the technique of choice.[16,36,37] Chromoendoscopy detected more lesions than white light also in our study. Given that a visible lesion will increase the probability of targeted biopsies, these were also associated with higher detection of advanced lesions. However, chromoendoscopy and targeted biopsies were only used in 25–38% and 20% of procedures, respectively, revealing a need for technical optimisation.

This study should be interpreted in the light of certain limitations as well as its strengths. The retrospective and multicentre design of the study entails inherent weaknesses. To avoid selection bias, the principal investigator of each centre undertook to collect all the patients who meet the inclusion and none of the exclusion criteria. To minimise varying data collection and interpretation protocols among centres, a well-defined protocol of the patients and variables to be collected was performed prior to data inclusion. Another drawback is a possible detection bias in which the true risk of colorectal lesions remains unknown in the subgroup of non-adherence patients who have not undergone any endoscopies. The relatively short follow-up period could have played a role in our findings, since the greatest increase in CRC risk appears 20–30 years after IBD diagnosis. Similarly, endoscopy has experienced major technology improvements during the study period that were not considered. However, most of the procedures were performed in the last 4 years, during which guidelines have not undergone big modifications. The major strength of our study lies in the large cohort, with a countrywide scope that includes different type of hospitals. This has yielded real-life results which will likely improve clinical practice.

Our findings demonstrate that endoscopic surveillance is associated with earlier detection of advanced colorectal lesions, nevertheless, adherence to ECCO guidelines is low in this Southern European population. Higher risk groups are correlated with poorer adherence to endoscopic recommendations. These results highlight the need to improve compliance with guidelines, especially in patients with risk factors.

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Author contributions: Ballester MP, Mesonero F and Minguez M were involved in study concept and design, data analysis and interpretation of the manuscript. Ballester MP also carried out drafting of the manuscript. All authors carried out acquisition of data, critical revision of the manuscript and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable no new data generated, or the article describes entirely theoretical research

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REFERENCES

1. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol*. 2015;12:205-217.
2. Flynn S, Eisenstein S. Inflammatory bowel disease presentation and diagnosis. *Surg Clin North Am*. 2019;99:1051-1062.
3. Lutgens MW, van Oijen MG, van der Heijden GJ, et al. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis*. 2013;19:789-799.
4. Keller DS, Windsor A, Cohen R, Chand M. Colorectal cancer in inflammatory bowel disease: review of the evidence. *Tech Coloproctol*. 2019;23:3-13.
5. Ording AG, Horváth-Puhó E, Erichsen R, et al. Five-year mortality in colorectal cancer patients with ulcerative colitis or Crohn's disease. *Inflamm Bowel Dis*. 2013;19:800-805.
6. Ou B, Zhao J, Guan S, Lu A. Survival of colorectal cancer in patients with or without inflammatory bowel disease: a meta-analysis. *Digest Dis Sci*. 2016;61:881-889.
7. Nadeem MS, Kumar V, Al-Abbasi FA, et al. Risk of colorectal cancer in inflammatory bowel diseases. *Sem Cancer Biol*. 2020;64:51-60.
8. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. *New Engl J Med*. 2015;372:1441-1452.
9. Burke KE, Nayor J, Campbell EJ, Ananthakrishnan AN, Khalili H, Richter JM. Interval Colorectal cancer in inflammatory bowel disease: the role of guideline adherence. *Digest Dis Sci*. 2020;65:111-118.
10. Ananthakrishnan AN, Cagan A, Cai T, et al. Colonoscopy is associated with a reduced risk for colon cancer and mortality in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2015;13:322-329.e1.

11. Bye WA, Ma C, Nguyen TM, Parker CE, Jairath V, East JE. Strategies for detecting colorectal cancer in patients with inflammatory bowel disease: A Cochrane systematic review and meta-analysis. *Am J Gastroenterol*. 2018;113:1801-1809.
12. Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology*. 2010;138:746-774.
13. Ooi CJ, Makharia GK, Hilmi I, et al. Asia Pacific Consensus Statements on Crohn's disease. Part 1: Definition, diagnosis, and epidemiology: (Asia Pacific Crohn's disease consensus—part 1). *J Gastroenterol Hepatol*. 2016;31:45-55.
14. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114:384-413.
15. Bromham N, Kallioinen M, Hoskin P, Davies RJ, Guideline Committee. Guideline Committee. Colorectal cancer: summary of NICE guidance. *BMJ*. 2020;2:m461.
16. Laine L, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastrointest Endos*. 2015;81:489-501.e26.
17. Annese V, Beaugerie L, Egan L, et al.; on behalf of ECCO European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis* 2015;9:945–65.
18. Cubiella J, Marzo-Castillejo M, Mascort-Roca JJ, et al. Clinical practice guideline. Diagnosis and prevention of colorectal cancer. 2018 Update. *Gastroenterol Hepatol*. 2018;41:585-596.
19. Sicilia B, Vicente R, Arias L, Echarri A, Zabana Y, Mañosa M, Beltrán B, Barreiro-de Acosta M, en nombre de GETECCU, on behalf of GETECCU. Recommendations of the Spanish Working Group on Crohn's disease and Ulcerative Colitis (Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa - GETECCU) on dysplasia screening in inflammatory bowel disease patients. *Gastroenterol Hepatol* 2021;44:435–447.
20. Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis*. 2013;7:982-1018.
21. Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileoanal Pouch Disorders. *J Crohns Colitis*. 2017;11:649-670.
22. Velayos FS, Liu L, Lewis JD, et al. Prevalence of colorectal cancer surveillance for ulcerative colitis in an integrated health care delivery system. *Gastroenterology*. 2010;139:1511-1518.
23. Van Rijn AF, Fockens P, Siersema PD, et al. Adherence to surveillance guidelines for dysplasia and colorectal carcinoma in ulcerative and Crohn's colitis patients in The Netherlands. *World J Gastroenterol*. 2009;15:226-230.
24. Verschuren EC, Ong DE, Kamm MA, Desmond PV, Lust M. Inflammatory bowel disease cancer surveillance in a tertiary referral hospital: attitudes and practice. *Int Med J*. 2014;44:40-49.
25. Santi G, Michetti P, Froehlich F, et al. Adherence to recommendations and quality of endoscopic colorectal cancer surveillance in long-standing ulcerative colitis. *Inflamm Intest Dis*. 2021;6:25-31.
26. Hardbord MS, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. part 2: current management. *J Crohns Colitis*. 2017;11:769-784.
27. Gomollón F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis*. 2017;11:3-25.
28. Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. *Gastrointest Endosc*. 2009;69:620-625.
29. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142:46-54.e42; quiz e30.
30. Mak WY, Zhao M, Ng SC, Burisch J. The epidemiology of inflammatory bowel disease: East meets west. *J Gastroenterol Hepatol*. 2020;35:380-389.
31. Jess T, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology* 2012;143:375-81.e1; quiz e13-4.
32. Castaño-Milla C, Chaparro M, Gisbert JP. Systematic review with meta-analysis: the declining risk of colorectal cancer in ulcerative colitis. *Aliment Pharmacol Therap*. 2014;39:645-659.
33. Malila N, Senore C, Armaroli P. European guidelines for quality assurance in colorectal cancer screening and diagnosis organisation. *Endoscopy*. 2012;44 Suppl 3:SE31-48.
34. Wintjens DSJ, Bogie RMM, van den Heuvel TRA, et al. Incidence and classification of postcolonoscopy colorectal cancers in inflammatory bowel disease: a Dutch population-based cohort study. *J Crohns Colitis*. 2018;12:777-783.
35. Singh K, Al Khoury A, Kurti Z, et al. High adherence to surveillance guidelines in inflammatory bowel disease patients results in low colorectal cancer and dysplasia rates, while rates of dysplasia are low before the suggested onset of surveillance. *J Crohns Colitis*. 2019;13:1343-1350.
36. Soetikno R, Subramanian V, Kaltenbach T, et al. The detection of nonpolypoid (flat and depressed) colorectal neoplasms in patients with inflammatory bowel disease. *Gastroenterology*. 2013 Jun;144:1349–52, 1352.e1-6.
37. Rubín de Célix C, Chaparro M, Moreno JA, Santander C, Gisbert JP. Colorectal cancer surveillance with chromoendoscopy in inflammatory bowel disease: results from a real-life experience. *Scand J Gastroenterol*. 2021;56:806-811.

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APPENDIX 1

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