



Endoscopic Surveillance in Serrated Polyposis Syndrome, Two or Three-Year Intervals: A Non-inferiority Randomized Trial

Jorge López-Vicente^{1,9} · Daniel Rodríguez-Alcalde^{1,2} · Luis Hernández Villalba³ · Patricia Pedregal Pascual⁴ · Luisa Adán Merino⁵ · Francisco Polo Ortiz⁶ · Xabier Bessa Caserras⁷ · Jose Carlos Marín Gabriel⁸ · David Varillas Delgado⁹ · the endoscopy for high-risk cancer conditions group of the Spanish Gastroenterological Association, Spanish Society of Digestive Endoscopy

Received: 19 January 2026 / Accepted: 13 March 2026 / Published online: 21 April 2026
© The Author(s) 2026

Abstract

Background Serrated polyposis syndrome, the most prevalent colonic polyposis, confers an increased colorectal cancer risk. Guidelines recommend close colonoscopy surveillance, but recent data suggest low neoplasia rates, supporting longer colonoscopy intervals.

Aims Compare advanced neoplasia incidence between two- and three-year surveillance.

Methods A multicentre, randomized non-inferiority trial was conducted (May 2021–November 2024) in six Spanish hospitals. Patients fulfilling the 2019 WHO criteria for serrated polyposis syndrome, including newly diagnosed individuals and those already under surveillance, with no advanced neoplasia and fewer than five relevant polyps at their previous colonoscopy, were randomized to surveillance at 2 or 3 years. The primary endpoint was advanced neoplasia incidence.

Results A total of 131 patients with serrated polyposis syndrome were included (47.3% women; mean age 66.1). Seventy-two were assigned to 2-year and 59 to 3-year colonoscopy. Among 771 resected lesions, 2.4% were advanced adenomas or advanced serrated polyps; no colorectal cancer was detected. The proportion of patients with advanced neoplasia in the surveillance colonoscopy was 6.9% (2-year) vs 13.6% (3-year), with no statistical difference ($p=0.208$) but with a risk difference of +6.7% (95% CI −4.1 to 17.5%) exceeding the pre-specified non-inferiority margin of +10%. Time since serrated polyposis syndrome diagnosis ≤ 3 years was associated with advanced neoplasia (OR 4.4; 95% CI 1.56–14.71; $p=0.024$).

Conclusions In patients with serrated polyposis syndrome, extending colonoscopy surveillance to a three-year compared with a two-year interval yielded inconclusive evidence regarding non-inferiority for advanced neoplasia incidence. The early years following serrated polyposis syndrome diagnosis were identified as a risk factor for advanced neoplasia.

Trial Registration Clinical Trial Registry ClinicalTrials.gov (NCT04906343). Date: 5–10-2021.

Keywords Polyp · Vigilance · Cancer · Surveillance

✉ Jorge López-Vicente
jlvicente@salud.madrid.org

¹ Department of Gastroenterology. Hospital, Universitario de Móstoles. Calle Doctor Luis Montes, s/n. 28935 – Móstoles (Madrid), Madrid, Spain

² Gastroenterology Department, Hospital Uni Department of Medical Specialties and Public Health, Faculty of Health Sciences, Universidad Rey Juan Carlos, Madrid, Spain

³ Gastroenterology Department, Hospital Santos Reyes, Aranda de Duero, Spain

⁴ Gastroenterology Department, Hospital Universitario Santa Creu I Sant Pau, Barcelona, Spain

⁵ Gastroenterology Department, Hospital Universitario Infanta Leonor, Madrid, Spain

⁶ Gastroenterology Department, Hospital Universitario de Basurto, Bilbao, Spain

⁷ Gastroenterology Department, Hospital Universitario del Mar, Barcelona, Spain

⁸ Gastroenterology Department, Hospital Universitario, 12 de Octubre, Madrid, Spain

⁹ Faculty of Health Sciences, Universidad Francisco de Vitoria, Madrid, Spain

Abbreviations

AA	Advanced adenoma
AN	Advanced neoplasia
CI	Confidence interval
CRC	Colorectal cancer
HD	High definition
HP	Hyperplastic polyps
OR	Odds ratio
SPS	Serrated polyposis syndrome
SP	Serrated polyps
SSL	Sessile serrated lesions
TSA	Traditional serrated adenomas
WHO	World Health Organization

Background

Serrated polyposis syndrome (SPS) is the most prevalent colorectal polyposis syndrome, ranging from 0.31 to 0.80% in faecal occult blood test or faecal immunochemical test-based screening programs and from 0.1 to 0.4% in colonoscopy-based programs [1] [2] [3] [4]. SPS is characterized by the presence of multiple colonic serrated polyps (SP), including hyperplastic polyps (HP), sessile serrated lesions (SSL) and traditional serrated adenomas (TSA). Diagnosis is based on clinical criteria established by the World Health Organization (WHO). The fifth edition of the *WHO Classification of Tumours of the Digestive System*, published in July 2019, defines SPS by either of the following criteria: Criterion I, ≥ 5 SP proximal to the rectum, all ≥ 5 mm in size, with at least 2 being ≥ 10 mm; or Criterion II, > 20 SP of any size distributed throughout the large bowel, with at least 5 located proximal to the rectum [5] [6].

SPS is associated with an increased risk of colorectal cancer (CRC) compared to the general population. Two large cohort studies have estimated a wide range of CRC incidence, from 15 to 29% [7] [8]. A 2022 meta-analysis reported an overall CRC risk of 19% (95% CI, 15.3–24.5%), with higher rates at the time of or prior to SPS diagnosis (14.7 [95% CI, 11.4–18.8%] and 7% [95% CI, 4.5–10.7%], respectively) [9]. However, the CRC incidence during surveillance appears lower than initially described, with a reported rate of 2.8% (95% CI, 1.8–4.4%) [9] [10].

Once SPS is diagnosed, all polyps ≥ 5 mm or with dysplastic appearance (adenoma, SSL or TSA) must be resected. Ideally, this should be achieved via polypectomy, although surgical resection may be required if the polyp burden cannot be managed endoscopically. After this clearing phase, close endoscopic surveillance is required. Long-term studies report a 5-year cumulative incidence of advanced neoplasia (AN)—CRC, advanced adenomas (AA), or advanced SP—of 21.6–44% during surveillance and after the clearing phase [11] [12] [13] [14]. In a prospective cohort of 142 patients

with a 10-year follow-up and regular colonoscopy (1–2 years), only one CRC case was detected. In this study, the incidence of AN at different surveillance rounds remained below 16% [14]. Risk factors identified for CRC or AN include smoking, proximal SSL, SP with dysplasia, AA, advanced SP, and SPS 2010 WHO criterion I [13]. These data had led to the proposal of personalized surveillance based on individual risk.

Due to limited evidence, surveillance recommendations differ across countries and scientific societies. The U.S. Multi-Society Task Force in 2012 advised annual colonoscopy [15], the American College of Gastroenterology in 2015 suggested 1–3 years [16], the Spanish Society of Gastroenterology in 2018 proposed 1–3 years [17] and the British Society of Gastroenterology in 2020 recommended 1–2 years surveillance [18], based on histology and the size of lesions detected during last colonoscopy.

The 2019 European Society of Gastrointestinal Endoscopy (ESGE) guideline on endoscopic management of polyposis syndromes, recommends surveillance intervals based on the findings of the most recent colonoscopy: 1 year after resection of ≥ 1 advanced adenoma or advanced SP or ≥ 5 relevant polyps (adenomas, SSL, TSA or HP ≥ 5 mm), and 2 years otherwise (strong recommendation and low quality of evidence) [19]. A prospective multicentre study of 271 patients with SPS (median follow-up 3.6 years) supported these recommendations, showing AN incidence of 15.6% with biennial vs 24.4% with annual surveillance (OR 0.57, 95% CI, 0.31–1.07; $p=0.08$). Only two CRC cases occurred, yielding 5-year incidence of 1.3%, while the 5-year cumulative AN incidence was 44% (95% CI, 37–52%). SPS WHO criterion I conferred higher AN risk than criterion III (2010 WHO criteria), whereas other factors were not significant. Notably, patients who had undergone prior surveillance colonoscopy before enrolment had lower risk of AN (HR 0.64, 95% CI, 0.41–0.99; $p=0.047$) [20].

Since biennial surveillance is not associated with increased AN, extending intervals beyond 2 years may be safe, effective and could alleviate the burden on endoscopy units. We therefore designed a non-inferiority randomized controlled trial to evaluate extended surveillance intervals in patients with SPS, specifically in individuals without AN or with fewer than five relevant polyps in their last colonoscopy. Patients were randomized to undergo colonoscopy at either two years or three years, and the primary outcome was the incidence of AN in each group.

Methods

Study Design

This multicentre randomized controlled trial (1:1) was conducted from May 2021 to November 2024 in six

Spanish hospitals, five with high-risk digestive cancer clinics. Patients fulfilling 2019 SPS WHO criteria and under surveillance were randomized to colonoscopy at 2 years (group A) or 3 years (group B). Randomization was performed and data were collected for all centres via the online database REDCap (Research Electronic Data Capture), an electronic data capture tool hosted by the Spanish Society of Digestive Endoscopy (SEED; www.wseed.es) [21]. The study complied with the Declaration of Helsinki, was approved by ethics committees (*Comité ético de investigación del Hospital Universitario de Móstoles. ID: 2021/005*) and registered at ClinicalTrials.gov (NCT04906343). Written informed consent was obtained from all individual participants included in the study. All authors had access to the study data and approved the final manuscript. This research was supported by a grant from the Spanish Society of Digestive Endoscopy Foundation (FSEED) in November 2021.

Inclusion and Exclusion Criteria

Eligible patients were aged ≥ 18 years with 2019 SPS WHO criteria I, II or both, having completed the clearing phase, and with < 5 relevant polyps and no AN at last colonoscopy. Thus, all patients had a recommended two-year surveillance interval according to ESGE guidelines before randomization [19]. Adequate bowel preparation (Boston Bowel Preparation Scale (BBPS) ≥ 2 in all segments [22] and cecal intubation in prior colonoscopy were required.

Exclusion criteria were patients with inflammatory bowel disease, other hereditary CRC syndromes (e.g., familial adenomatous polyposis, Lynch syndrome, Peutz-Jeghers syndrome, Cowden syndrome, juvenile polyposis syndrome), total colectomy, a piecemeal-resected lesion or invasive cancer at previous colonoscopy, and colonoscopy outside the scheduled window (± 3 months).

Definitions:

- AN: AA or advanced SP.
- Relevant polyps: SSL or adenomas (any size), TSA or HP ≥ 5 mm.
- Clearing phase: resection of polyps ≥ 5 mm or with dysplasia (adenomas, TSA, SSL) [19].
- Time since SPS diagnosis: defined as the interval between the initial clinical diagnosis of SPS and study inclusion.

Clinical and Demographic Characteristics

Collected variables were age, sex, smoking history, SPS criteria, personal CRC history, prior surgery, history of AA or advanced SP, and number of surveillance colonoscopies after clearing phase.

Colonoscopy Procedures

High-definition (HD) endoscopes were used in all procedures, with chromoendoscopy, virtual chromoendoscopy or white light at endoscopist discretion. Bowel preparation protocols followed each centre's standard practice and an adequate bowel preparation was defined as BBPS ≥ 2 in all segments [22]. Sedation was administered at the discretion of the endoscopist or anaesthesiologist. Polyps were classified according to the Paris morphology classification [23]. Location, size, and resection technique were recorded. Complications, including bleeding, perforation, or cardiorespiratory events occurring during the procedure or within the first month afterward, were documented. Only events requiring endoscopic intervention, hospitalization, or surgery were recorded.

Histopathology

Tissue specimens were processed by gastrointestinal pathologists using the Vienna classification for gastrointestinal epithelial neoplasia [24]. Invasive cancer was defined as neoplastic extension into the submucosa or beyond. Polyp classification was based on WHO criteria [25]:

- SP: HP, SSL (with or without dysplasia) and TSA.
- AA: Adenomas ≥ 10 mm, villous component and/or with high-grade dysplasia.
- Advanced SP: SP > 10 mm and/or with dysplasia.
- AN: Includes AA, Advanced SP and CRC.

Study Outcomes

Primary: compare AN incidence between 2- and 3-year groups with a non-inferiority analysis.

Secondary: compare relevant polyps incidence, identify risk factors for AN and changes in surveillance recommendations based on ESGE guidelines.

Sample Size Calculation

Based on a Dutch study by Bleijenberg et al., reporting a 15.6% AN incidence at two-year colonoscopy in low risk patients [20], the non-inferiority margin between the 2 years interval and the 3 years strategy was set to + 10%. A total of 136 patients (68 per group) were required to achieve 80% power ($\beta = 0.2$) to demonstrate non-inferiority, with a one-sided 0.025 contrast (type I error) and a 5% significance level, accounting for 10% expected losses.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 25.0 for Windows (IBM Corp., 2012. NY: IBM Corp., USA). Quantitative variables were expressed in mean and standard deviation ($\pm$ SD) and qualitative variables were expressed in frequency (%). In the non-inferiority analysis a 1-sided confidence interval approach was used, with a preestimated margin of non-inferiority (Δ) of +10%.

Two-stage analyses were performed using Fisher's test, χ^2 test, and multiple logistic regression analysis to identify the variables that predicted AN. Factors reaching $p < 0.20$ in univariate analysis were analysed using a multivariate logistic regression test. Univariate analysis and multivariate logistic regression results were summarized as the odds ratio (OR) with 95% confidence interval (CI) for the OR. A p -value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 145 patients were enrolled in the study, 74 randomized to 2-year follow-up colonoscopy (Group A) and 71 to

3-year follow-up (Group B). The study flow-chart following the Consolidated Standards of Reporting Trials (CONSORT) guidelines is presented in Fig. 1. Fourteen patients were excluded after randomization: 4 due to inadequate bowel preparation and 10 because they were lost in follow-up or underwent colonoscopy outside surveillance window (4% in the 2-year and 16.9% in the 3-year group). This left 131 patients for the data analysis, 72 in Group A and 59 in Group B.

Mean age was 66.1 years (range 33.4–79.6), and 47.3% were women. At inclusion, 20 patients (15.3%) met WHO criterion I, 88 (67.2%) criterion II, and 23 (17.5%) both. Ten patients (7.6%) had a prior history of CRC.

SPS diagnosis was established a mean of 4.9 years before inclusion (range 1–11). Patients had a median of 6.5 colonoscopies (range 2–22) before enrolment, and 2.9 surveillance procedures after the clearing phase (range 0–7). Only 7 patients (5.3%) were randomized immediately after the clearing phase, while 105 (80.2%) had ≥ 2 surveillance colonoscopies before randomization. Baseline characteristics of patients by group are detailed in Table 1.

Procedures and Adverse Events

All procedures used HD technology. Virtual chromoendoscopy was applied in 30 cases (23.8%), chromoendoscopy

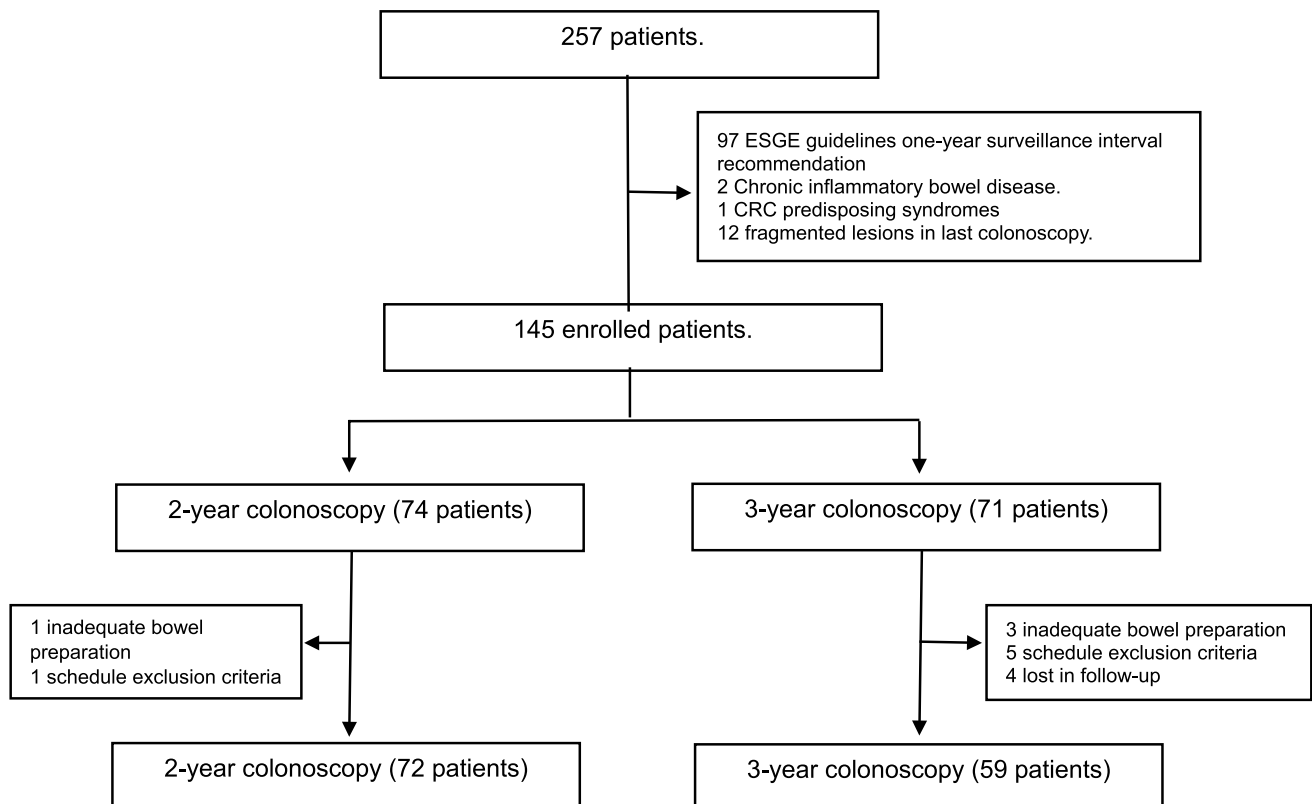


Fig. 1 Patients' flowchart

with indigo carmine in 69 (53.1%), and white light alone in 30 (23.1%). No adverse events as bleeding, perforation or cardiopulmonary complications were reported. Procedure duration and withdrawal time were similar between groups (Table 2).

Lesions and Outcomes

Across 124 patients, 771 polyps were resected, and 7 patients had no lesion. Twelve polyps lacked histology, and 140 (18.3%) were normal tissue, leaving 619 lesions for analysis. The morphological and histological characteristics of polyps are shown in Table 2. Among these, 15 (2.4%) polyps were AN—6 in group A (1.7%) and 9 in group B (3.4%), $p=0.177$. Fourteen were advanced SP and one was an AA; no CRC was detected.

Relevant polyps (SSL, adenomas, TSA or HP ≥ 5 mm) accounted for 289 (46.7%): 170 (48.2%) in group A and 119 (44.7%) in group B, $p=0.398$. Mean polyp size was similar between the two groups: 3.74 mm (95% CI 3.52–3.94) vs 3.77 mm (95% CI 3.57–3.96), $p=0.819$; as the mean number of polyps per colonoscopy 5.9 (95% CI 5.1–6.8) vs 5.3 (95% CI 4.4–6.3), $p=0.336$, group A and group B respectively.

Table 3 presents the distribution of lesions detected per patient in each surveillance group, including AN and relevant polyps.

The overall incidence of patients with at least one AN was 9.9% (95% CI, 4.8–15.1%), with 5/72 patients (6.9%) in group A and 8/59 (13.6%) in group B, $p=0.208$. The risk difference was +6.7% (95% CI, −4.1 to 17.5; $p=0.27$). Since the upper bound of the confidence interval exceeds the pre-specified non-inferiority margin of +10%, non-inferiority of the 3-year strategy could not be established. Therefore, results regarding non-inferiority analysis are inconclusive [26] Figure 2.

Patients with ≥ 5 relevant polyps were 18.1% in group A vs 15.3% in group B, with no statistical difference (OR 0.81, 95% CI, 0.32–2.07; $p=0.670$).

According to ESGE polypoid guideline recommendations, 30/131 patients (22.9%) should return to a 1-year surveillance interval, due to the detection of at least one AN or ≥ 5 relevant polyps, with no difference between groups (22.2% in group A vs 23.7% in group B, $p=0.838$); Fig. 3.

A post hoc power analysis yielded a statistical power of 33.8%.

Association Between Advanced Neoplasia and Patient Characteristics

Table 4 shows associations between patient variables and AN. In univariate analysis, shorter time since SPS diagnosis and fewer number of colonoscopies after the clearing phase significantly predicted AN. Patients diagnosed from SPS ≤ 3 years had a 7.1-fold higher risk (95% CI,

Table 1 Baseline patient characteristics by surveillance group

	Group A (2 years)	Group B (3 years)
SPS WHO criteria (%):		
II	63.9	71.2
I	15.3	15.3
I+II	20.8	13.6
Women (%)	55.6	37.3
Age (years)	67.1	64.9
Smoking history (%)		
Never	15.3	18.5
Current	36.1	39.0
Former	48.8	42.5
Personal history of CRC (%)	8.3	6.8
Partial colectomy (%)	9.7	6.8
Median number of colonoscopies before randomization	6.5	6.4
Median number of colonoscopies after the clearing phase	2.8	2.9
Patients with previous AA (%)	36.6	43.1
Patients with previous advanced SP (%)	59.2	55.2
Years after diagnosis of SPS (median)	4.7	5.2

SPS serrated polyposis syndrome, WHO world health organization, CRC colorectal cancer, AA advanced adenoma, SP serrated polyps

Table 2 Polyp characteristics in all colonoscopies by surveillance group and time of procedures.

	Group A (2 years)	Group B (3 years)	<i>p</i> (sig < 0.05)
Histology			
Total polyps	412	347	0.002
Normal tissue	59 (14.2%)	81 (23.1%)	
HP	205 (49.3%)	171 (48.9%)	
SSL without dysplasia	44 (10.6%)	26 (7.4%)	
SSL with dysplasia	0 (0%)	4 (1.1%)	
Adenoma LGD	104 (25.0%)	65 (18.6%)	
Adenoma HGD	0 (0%)	0 (0%)	
CRC	0 (0%)	0 (0%)	
Total polyps with histology	353	266	
Advanced adenomas	0 (0%)	1 (0.4%)	0.249
Advanced SP	6 (1.7%)	8 (3.0%)	0.279
Advanced neoplasia	6 (1.7%)	9 (3.4%)	0.177
Relevant polyps	170 (48.2%)	119 (44.7%)	0.398
Location			
Total polyps with histology	353	266	0.011
Ascending colon	79 (22.4%)	42 (15.8%)	
Transverse colon	89 (25.2%)	73 (27.4%)	
Descending colon	64 (18.1%)	38 (14.3%)	
Sigmoid colon	88 (24.9%)	66 (24.8%)	
Rectum	33 (9.3%)	47 (17.7%)	
Morphology (Paris classification)			
Total polyps with histology	353	266	0.020
0-Is	24 (6.8%)	27 (10.2%)	
0-Ip	0 (0%)	0 (0%)	
0-IIa	278 (78.8%)	218 (78.8%)	
0-IIb	51 (14.4%)	21 (7.9%)	
0-IIc	0 (0%)	0 (0%)	
0-III	0 (0%)	0 (0%)	
Mean size (SD) mm	3.7 (1.9)	3.8 (1.6)	0.819
Number of polyps per colonoscopy (mean)	5.9	5.3	0.336
Total time of colonoscopy (minutes)	28.2	26.3	0.297
Withdrawal time during colonoscopy (minutes)	22.5	20.6	0.267

CRC colorectal cancer, *HGD* high-grade dysplasia, *HP* hyperplastic polyp, *LGD* low-grade dysplasia, *SSL* sessile serrated lesion, *SP* serrated polyp, *SD* standard deviation

Table 3 Distribution of lesions per patient by surveillance group

	Group A (2 years)	Group B (3 years)	risk difference (95% CI, −4.1 to 17.5)	<i>p</i> (sig < 0.05)
Patients with at least one:	5 (6.9%)	8 (13.6%)	+ 6.7%	0.208
Advanced neoplasia	13 (18.1%)	9 (15.3%)		0.670
Relevant polyp SSL without dysplasia	16 (22.2%)	7 (11.9%)		0.121
SSL with dysplasia	0 (0%)	2 (3.4%)		0.115
Advanced adenoma	0 (0%)	1 (1.7%)		0.267
Advanced SP	5 (6.9%)	7 (11.9%)		0.331
Total patients	72	59		

SSL sessile serrated lesion, *SP* serrated polyp

Forest Plot – Risk Difference in Advanced Neoplasia (3y vs 2y)

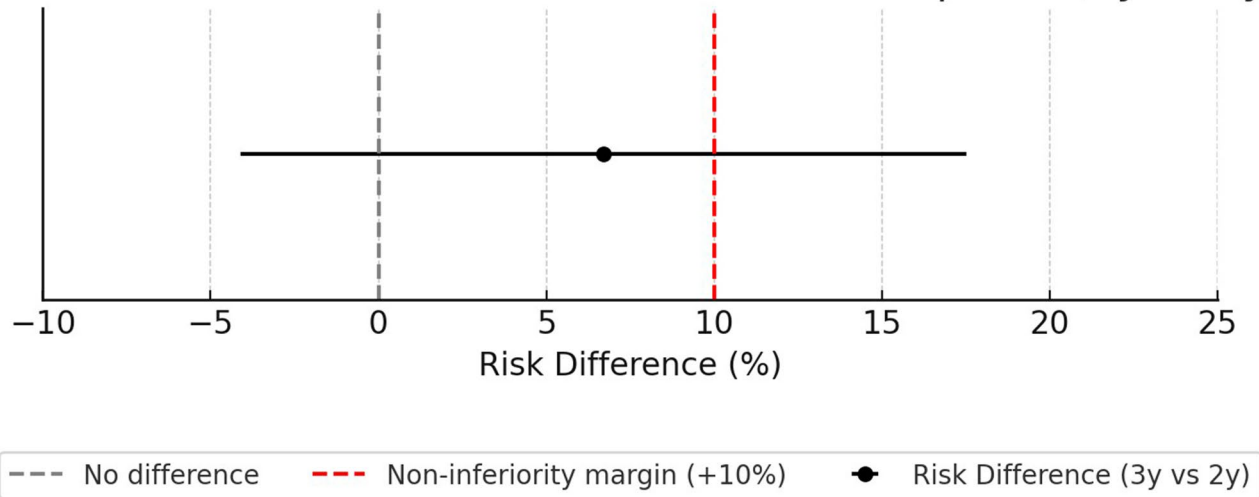


Fig. 2 Non-inferiority analysis. Risk difference of advanced neoplasia

Fig. 3 Colonoscopy recommendation based on lesions detected

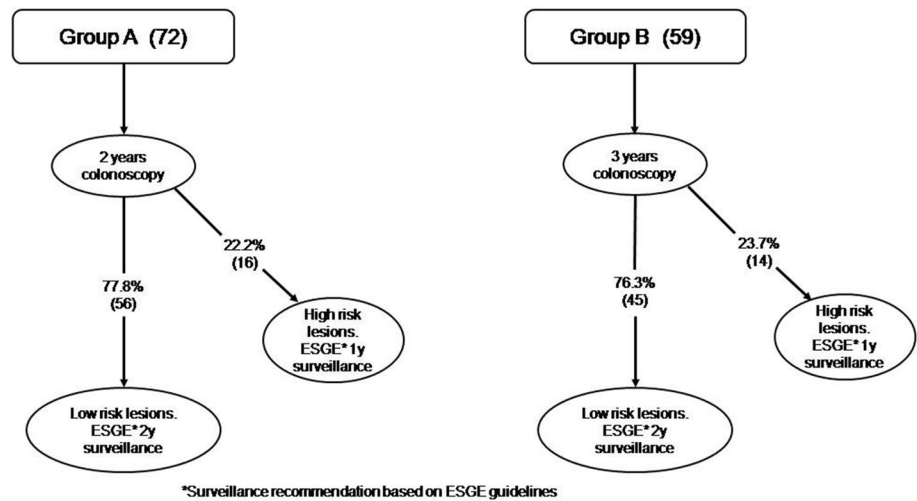


Table 4 Predictors of advanced neoplasia and relevant polyps using univariate analysis

	Advanced neoplasia		Relevant polyps	
	OR (95% CI)	p value	OR (95% CI)	p value
Gender (male)	1.05 (0.33–3.32)	0.929	1.72 (0.67–4.43)	0.259
Age (> 65 years)	0.75 (0.24–2.36)	0.636	1.51 (0.57–3.99)	0.408
Smoking (former or current)	1.54 (0.39–6.21)	0.523	2.15 (0.74–6.40)	0.149
WHO criterion at study inclusion (I or I + II)	1.88 (0.59–5.97)	0.281	0.40 (0.13–1.26)	0.109
SPS diagnosis (≤ 3 years)	7.05 (2.03–24.12)	<0.001	2.11 (1.02–4.48)	0.048
Colonoscopies after clearing phase (< 2)	3.11 (1.05–9.58)	0.036	1.66 (0.77–3.56)	0.191
Previous colonoscopy (> 5)	0.57 (0.18–1.79)	0.330	1.28 (0.50–3.30)	0.617
Personal history of CRC (yes)	0.89 (0.70–1.44)	0.275	0.53 (0.06–4.40)	0.550
Previous advanced adenoma (yes)	1.60 (0.49–5.27)	0.436	1.87 (0.73–4.79)	0.188
Previous advanced SP (yes)	4.14 (0.87–19.73)	0.056	2.08 (0.75–5.76)	0.154

WHO World Health Organization, SPS serrated polyposis syndrome, CRC colorectal cancer, SP serrated polyps

Table 5 Multivariate logistic regression for advanced neoplasia and relevant polyps

Variable for advanced neoplasia	Univariate analysis		Multivariate analysis	
	OR (95%CI)	<i>p</i> value	OR (95%CI)	<i>p</i> value
SPS diagnosis (≤ 3 years)	7.05 (2.03–24.12)	< 0.001	4.35 (1.56–14.71)	0.024
Colonoscopy after clearing phase (< 2)	3.11 (1.05–9.58)	0.036	1.91 (0.28–13.26)	0.513
Previous advanced SP (yes)	4.14 (0.87–19.73)	0.056	2.64 (0.52–13.43)	0.242
Variable for relevant polyps	Univariate analysis		Multivariate analysis	
	OR (95%CI)	<i>p</i> value	OR (95%CI)	<i>p</i> value
Smoking (former or current)	2.15 (0.74–6.41)	0.149	1.79 (0.65–4.43)	0.196
WHO criterion at study inclusion (I or I+II))	0.40 (0.13–1.26)	0.109	0.88 (0.17–2.33)	0.463
SPS diagnosis (≤ 3 years)	2.11 (1.02–4.48)	0.048	2.04 (1.18–3.93)	0.033
Colonoscopy after clearing phase (< 2)	1.66 (0.77–3.56)	0.191	1.22 (0.30–3.15)	0.784
Previous advanced adenoma (yes)	1.87 (0.73–4.79)	0.188	1.75 (0.69–5.25)	0.263
Previous advanced SP (yes)	2.076 (0.75–5.76)	0.154	1.87 (0.71–4.21)	0.206

WHO World Health Organization, SPS serrated polyposis syndrome, CRC colorectal cancer, SP serrated polyps

2.03–24.12; $p < 0.001$), and those with < 2 colonoscopies after clearing phase had a 3.1-fold higher risk (95% CI, 1.05–9.58; $p = 0.036$). A history of advanced SP also suggested increased risk of AN (OR 4.1, 95%CI, 0.87–19.73; $p = 0.056$), but not reaching statistical significance.

In multivariate analysis (Table 5), only time since SPS diagnosis remained an independent predictor of AN: patients diagnosed from SPS (≤ 3 years had 4.4-fold greater risk (95% CI, 1.56–14.71; $p = 0.024$).

Association Between Relevant Polyps and Patient Characteristics

The statistical analyses of predictors for relevant polyps are presented in Table 4. In univariate analysis, time since SPS diagnosis was a significant predictor of relevant polyps: patients diagnosed (≤ 3 years had 2.11-fold higher risk (95% CI, 1.02–4.48; $p = 0.048$).

In multivariate analysis (Table 5), time since SPS diagnosis remained a significant predictor for relevant polyps: patients diagnosed ≤ 3 years had 2.04-fold greater risk (95% CI, 1.18–3.93; $p = 0.033$).

Discussion

In this randomized multicentre trial, non-inferiority of the 3-year follow-up strategy could not be established as the upper bound of the risk difference CI exceeded the pre-specified non-inferiority margin of + 10%, the study was significantly underpowered, likely due to the high drop-out rate in the 3-year group. The incidences of AN in the surveillance colonoscopy (6.9% in 2-year group vs 13.6%

in 3-year group) were lower than expected based on previous literature. It is important to highlight that, in our study, patients did not present AN on the previous colonoscopy; therefore, they could be considered a low-risk group for AN. Bleijenbergh et al., in a single-centre cohort of patients with SPS with a prospective 10-year follow-up and surveillance intervals of either 1 or 2 years, reported a relatively stable incidence of AN ranging from 8.7 to 24.2% [14]. Another single-centre cohort from Spain reported a 3-year cumulative AN incidence at 12.1% in 109 monitored patients, which aligns with our cohort [13]. The largest prospective study, involving 271 patients with SPS with a median follow-up of 3.6 years, described a cumulative AN incidence of 44% at five years [20]. This study suggested that AN incidence declines after surveillance, with lower risk in patients who had at least one prior colonoscopy (HR 0.64, 95% CI 0.41 to 0.99, $p = 0.047$). In that cohort, 31% of patients had prior follow-up, whereas 69% underwent their first surveillance colonoscopy after inclusion. In our study, only 7 patients (5.3%) had their first surveillance colonoscopy after inclusion—considerably lower than in the Bleijenbergh study. Even more, 105 of 131 patients (80.2%) had undergone at least two surveillance colonoscopies after the clearing phase. In univariate analysis, patients with fewer than two colonoscopies after the clearing phase had over threefold higher AN risk, even though this association was not confirmed in multivariable analysis. Moreover, in our study, time since SPS diagnosis was also associated with AN detection at surveillance colonoscopy. Our findings suggest that patients with longer follow-up, longer interval since SPS diagnosis and more colonoscopies after the clearing phase have a lower risk of developing AN. Given that most participants were already under prolonged surveillance before enrolment and

had no AA or advanced SP in their last colonoscopy, these two factors may explain the slightly lower incidence of AN observed in our cohort.

Several risk factors have been linked to CRC and AN incidence in retrospective studies, including the presence of SP with dysplasia, previous AA or advanced SP, and fulfilling both SPS WHO criteria I and III (2019 criteria II) [7] [8] [12]. Although these retrospective studies included a large number of patients, their findings were not corroborated in a subsequent prospective study [14]. Our results did not establish a relationship between these risk factors and AN occurrence. Gender, smoking status, age, prior AN, and SPS WHO criteria were not associated with AN detection. However, patients with prior advanced SP had a higher proportion of AN compared to those without (13.5% vs 3.6%), a difference approaching statistical significance [OR: 4.14 (95%IC: 0.87–19.73), $p=0.056$]. While our sample size was relatively large, it may not have been sufficiently powered to detect associations between risk factors and AN.

Meeting 2019 SPS criteria I or I+II in our study was linked to nearly double the AN risk (14 vs 8%), but without statistical significance [OR: 1.88, (95% CI 0.59–5.97), $p=0.28$]. These data are comparable with larger retrospective and prospective cohorts that found significant higher AN incidence in patients meeting criteria I or I+III (2019 criteria II) [13] [20]. However, those studies were mainly retrospective and focused on 5-year cumulative AN incidence, while ours assessed 2- and 3-year intervals. Our cohort also included more patients meeting only SPS criteria II (67.2%) compared to other studies (36.5–45.3%) [7] [20]. Perhaps with a larger cohort including more SPS criteria I patients, differences might reach significance, potentially confirming a higher AN risk in these individuals. Notably, the only meta-analysis on CRC risk in SPS found no differences across WHO criteria [9].

In our cohort, 10 of 131 patients (7.6%) had a history of CRC, lower than reported in the literature. A meta-analysis by Müller et al. estimated a 14.7% CRC risk prior to SPS diagnosis and 2.8% during surveillance [9]. No cases of CRC were detected at either the 2- or 3-year follow-up in our study, consistent with previous findings from two retrospective series: one including 60 patients (mean follow-up, 2.1 years) and another with 96 patients (median, 3.6 years), as well as a single-centre prospective study of 41 patients followed for 3.1 years, all of which reported no incident CRC cases [11] [27] [28]. In a Dutch prospective cohort (> 10 years), only one CRC occurred, yielding a 5-year incidence of 1.0% (95% CI, 0–2.9%) [14]. These findings support the low risk of CRC during surveillance in patients with SPS, particularly with the use of HD-endoscopy and specialized endoscopist care.

In recent years, greater awareness of SPS has enhanced early detection in screening programs and routine

colonoscopies, allowing diagnosis as soon as WHO criteria are met and potentially preventing the development of AN. All participating centres in our study were secondary hospitals that do not receive patients from other institutions. This differs from specialized referral centres, where selection bias may lead to a higher proportion of aggressive SPS phenotypes and, consequently, increased AN incidence.

A total of 771 polyps were resected across 131 colonoscopies, with a mean of 5.9 polyps per procedure. In comparison, another long-term follow-up study [14] reported 1308 polypectomies across 447 colonoscopies, with a mean of 2.9 polyps per procedure. Most resected polyps in our study were small, distributed throughout the colon and with highest frequency in the transverse colon (28%). On the other hand, 18.3% of resected polyps were histologically normal tissue, data often not reported. This suggests that the high number of small polyps may have led to the resection of lesions that lacked histological abnormalities. Given that 67.2% of our patients met only SPS WHO criteria II and they typically present with numerous small polyps, this could have contributed to the high rate of small and normal-tissue resections. Importantly, no carcinoma or high-grade dysplasia was detected in any colonoscopy.

An additional finding was the significantly higher proportion of resected lesions with normal histology in the 3-year surveillance group compared with the 2-year group. This difference may reflect a more cautious endoscopic approach in patients undergoing longer surveillance intervals, resulting in a lower threshold for resection of subtle lesions. Such behavior could partly explain both the increased resection of non-neoplastic tissue and the higher detection of AN observed in the 3-year group.

The absence of adverse events was likely due to the study's sample size, which may not have been sufficient to capture such occurrences, and also to the high number of diminutive lesions resected. The estimated incidence of post-polypectomy bleeding in different series is approximately 0.6–1.8% [29], while perforation rates following colonoscopic mucosal resection range from 0.08 to 0.11% [30, 31]. However, this does not negate the risks and inconveniences associated with colonoscopy surveillance, including the potential impact on patients' daily activities [31].

Withdrawal time was consistently high across procedures, with a mean ≥ 20 min in both groups. Chromoendoscopy—either virtual or with indigo carmine—was employed in over 75% of colonoscopies, and all procedures were performed using HD technology. This underscores the high quality and reliability of surveillance colonoscopies in our study, in line with quality guidelines.

Our findings indicate that time since SPS diagnosis may be relevant for risk stratification during surveillance. The

independent association between a shorter time since SPS diagnosis (≤ 3 years) and AN suggests that the early surveillance period may require closer follow-up. In contrast, in patients without AN after an initial stable surveillance period of at least three years, a cautious consideration of extended surveillance intervals may be reasonable. Nevertheless, this approach should be interpreted conservatively and requires validation in further prospective studies.

Strengths and Limitations

Our study has several strengths. It was a randomized, controlled, multicentre trial conducted in regional hospitals, most with dedicated high-risk digestive cancer clinics. All patients met the updated 2019 SPS WHO criteria I or II, making this the first prospective study to apply these definitions, and underwent high-quality endoscopic procedures, ensuring reliable results.

Nonetheless, there are limitations. The study was conducted only in Spain, with a higher proportion of patients fulfilling SPS criteria II than in previous cohorts. Follow-up was restricted to a single surveillance round of 2 or 3 years, limiting conclusions on long-term AN incidence. Moreover, the post hoc power analysis yielded a statistical power of only 33.8%, well below the commonly accepted 80% threshold, indicating a low probability of detecting true effects in this sample, largely due to patient loss in the 3-year group and reflecting an underestimated sample size.

Conclusion

In conclusion, extending endoscopic surveillance to three years in patients with SPS could not be demonstrated as non-inferior to the standard two-year strategy for AN detection, the study was significantly underpowered. Although some authors suggest longer intervals for selected patients, our results could not currently support this approach. Patients with SPS continue to carry an elevated risk of AN or CRC during follow-up, although lower than previously reported. This risk is greatest in the initial years after SPS diagnosis, and our findings indicate it may decrease beyond the third year. Such a trend could support a de-intensified surveillance strategy for selected subgroups, especially in these low-risk patients without advanced neoplasia and with fewer than 5 relevant lesions in the last colonoscopy. However, additional long-term studies and adequately powered randomized controlled trials, with multiple surveillance rounds, are necessary to more accurately define the cumulative risk under the revised 2019 SPS WHO criteria.

Author Contributions All authors contributed to the study data collection. Study conception and design was performed by J.L.V, D.R.A, D.V.D and J.C.M.G. Material preparation and analysis were performed by J.L.V, D.V.D and J.C.M.G. The first draft of the manuscript was written by J.L.V and D.R.A and all authors commented on previous versions of the manuscript. J.L.V prepared Figs. 1 and 3, tables 1 and 2. D.V.D prepared tables 3 and 4. J.C.M.G prepared Fig. 2. All authors reviewed and approved the final manuscript.

Funding Open Access funding provided thanks to the CRUE-CSIC agreement with Springer Nature. This research was supported by a grant from the Spanish Society of Digestive Endoscopy Foundation (FSEED) in November 2021.

Data Availability The data generated and analyzed during this study are stored in a restricted-access database (REDCap – Research Electronic Data Capture) hosted by the Spanish Society of Digestive Endoscopy (SEED; www.wseed.es). Data are available upon reasonable request and with the consent of the corresponding author.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval The study complied with the Declaration of Helsinki, was approved by ethics committees (*Comité ético de investigación del Hospital Universitario de Móstoles*. ID: 2021/005).

Consent to participate Written informed consent was obtained from all individual participants included in the study.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

1. van Herwaarden YJ, Versteegen MHP, Dura P et al. Low prevalence of serrated polyposis syndrome in screening populations: a systematic review. *Endoscopy*. 2015;47:1043–1049. <https://doi.org/10.1055/s-0034-1392411>.
2. Rivero-Sanchez L, Lopez-Ceron M, Carballal S et al. Reassessment colonoscopy to diagnose serrated polyposis syndrome in a colorectal cancer screening population. *Endoscopy*. 2017;49:44–53. <https://doi.org/10.1055/s-0042-115640>.
3. IJsspeert JEG, Bevan R, Senore C et al. Detection rate of serrated polyps and serrated polyposis syndrome in colorectal cancer screening cohorts: a European overview. *Gut*. 2017;66:1225–1232.
4. Colussi D, Zagari RM, Morini B et al. Prevalence of serrated polyposis syndrome in an FIT-based colorectal cancer screening

- cohort in Italy. *Gut*. 2017;66:1532–1533. <https://doi.org/10.1136/gutjnl-2016-313063>.
5. Nagtegaal ID, Odze RD, Klimstra D et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76:182–188. <https://doi.org/10.1111/his.13975>.
6. Dekker E, Bleijenberg A, Balaguer F et al. Update on the world health organization criteria for diagnosis of serrated polyposis syndrome. *Gastroenterology*. W.B. Saunders. 2020;158:1520–1523.
7. Carballal S, Rodríguez-Alcalde D, Moreira L et al. Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study. *Gut*. 2016;65:1829–1837. <https://doi.org/10.1136/gutjnl-2015-309647>.
8. Ijspeert JEG, Rana SAQ, Atkinson NSS et al. Clinical risk factors of colorectal cancer in patients with serrated polyposis syndrome: a multicentre cohort analysis. *Gut*. 2017;66:278–284.
9. Muller C, Yamada A, Ikegami S et al. Risk of colorectal cancer in serrated polyposis syndrome: a systematic review and meta-analysis. *clinical gastroenterology and hepatology. Clin Gastroenterol Hepatol*. 2022;20:622–630.
10. Hyman NH, Anderson P, Blasyk H. Hyperplastic polyposis and the risk of colorectal cancer. *Dis Colon Rectum*. 2004;47:2101–2104. <https://doi.org/10.1007/s10350-004-0709-6>.
11. Hazewinkel Y, Tytgat KMAJ, van Eeden S et al. Incidence of colonic neoplasia in patients with serrated polyposis syndrome who undergo annual endoscopic surveillance. *Gastroenterology*. 2014;147:88–95. <https://doi.org/10.1053/j.gastro.2014.03.015>.
12. Rodríguez-Alcalde D, Carballal S, Moreira L et al. High incidence of advanced colorectal neoplasia during endoscopic surveillance in serrated polyposis syndrome. *Endoscopy*. 2019;51:142–151. <https://doi.org/10.1055/a-0656-5557>.
13. Rodríguez-Alcalde D, Castillo-López G, López-Vicente J, Hernández L, Lumberras-Cabrera M, Moreno-Sánchez D. Long-term incidence of advanced colorectal neoplasia in patients with serrated polyposis syndrome: Experience in a single academic centre. *Cancers (Basel)*. 2021;13:1–12. <https://doi.org/10.3390/cancers13051066>.
14. Bleijenberg AGC, Ijspeert JEG, Hazewinkel Y et al. The long-term outcomes and natural disease course of serrated polyposis syndrome: over 10 years of prospective follow-up in a specialized center. *Gastrointest Endosc*. 2020;92:1098–1107. <https://doi.org/10.1016/j.gie.2020.04.068>.
15. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US multi-society task force on colorectal cancer. *Gastroenterology*. 2012;143:844–857. <https://doi.org/10.1053/j.gastro.2012.06.001>.
16. Syngal S, Brand RE, Church JM et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*. 2015;110:223–262 (**quiz 263**).
17. 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.
18. Monahan KJ, Bradshaw N, Dolwani S et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut*. 2020;69:411–444. <https://doi.org/10.1136/gutjnl-2019-319915>.
19. Van Leerdam ME, Roos VH, Van Hooft JE et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy. Georg Thieme Verlag*. 2019;51:877–895. <https://doi.org/10.1055/a-0965-0605>.
20. Bleijenberg AGC, Ijspeert JEG, Van Herwaarden YJ et al. Personalised surveillance for serrated polyposis syndrome: Results from a prospective 5-year international cohort study. *Gut*. 2020;69:112–121. <https://doi.org/10.1136/gutjnl-2018-318134>.
21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381. <https://doi.org/10.1016/j.jbi.2008.08.010>.
22. Calderwood AH, Jacobson BC. Comprehensive validation of the Boston Bowel Preparation Scale. *Gastrointest Endosc*. 2010;72:686–692. <https://doi.org/10.1016/j.gie.2010.06.068>.
23. Endoscopic Classification Review Group. Update on the paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy*. 2005;37:570–578. <https://doi.org/10.1055/s-2005-861352>.
24. Schlemper RJ, Riddell RH, Kato Y et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut*. 2000;47:251–255. <https://doi.org/10.1136/gut.47.2.251>.
25. Crockett SD, Nagtegaal ID. Terminology, molecular features, epidemiology, and management of serrated colorectal neoplasia. *Gastroenterology. W.B. Saunders*. 2019;157:949–966.
26. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG, CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308:2594–2604.
27. MacPhail ME, Thygesen SB, Patel N, Broadley HM, Rex DK. Endoscopic control of polyp burden and expansion of surveillance intervals in serrated polyposis syndrome. *Gastrointest Endosc*. 2019;90:96–100. <https://doi.org/10.1016/j.gie.2018.11.016>.
28. Parry S, Burt RW, Win K et al. Reducing the polyp burden in serrated polyposis by serial colonoscopy: the impact of nationally coordinated community surveillance. *NZMJ*. 2017;130:57–67.
29. Sengupta N, Feuerstein JD, Jairath V et al. Management of Patients With Acute Lower Gastrointestinal Bleeding: An Updated ACG Guideline. *Am J Gastroenterol*. 2023;118:208–231. <https://doi.org/10.14309/ajg.0000000000002130>.
30. Rex DK, Anderson JC, Butterly LF et al. Quality Indicators for Colonoscopy. *Am J Gastroenterol*. 2024;119:1754–1780. <https://doi.org/10.14309/ajg.0000000000002972>.
31. Ferlitsch M, Hassan C, Bisschops R et al. Colorectal polypectomy and endoscopic mucosal resection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2024. *Endoscopy*. 2024;56:516–545. <https://doi.org/10.1055/a-2304-3219>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.