Panchromoendoscopy Increases Detection of Polyps in Patients With Serrated Polyposis Syndrome

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BACKGROUND & AIMS: **Serrated polyposis syndrome (SPS), characterized by multiple and/or large proximal serrated lesions, increases the risk of colorectal cancer. Serrated lesions often are missed during colonoscopy but panchromoendoscopy can increase their detection in an average-risk population. We performed a randomized controlled study to determine the efficacy of panchromoendoscopy in detection of polyps in patients with SPS.**

METHODS: **Patients with SPS (n = 86 patients) underwent tandem high-definition (HD) colonoscopies from February 2015 through July 2016 at 7 centers in Spain. Patients were assigned randomly to groups that received 2 HD white-light endoscopy examinations (HD-WLE group; n = 43) or HD-WLE followed by 0.4% indigo carmine panchromoendoscopy (HD-CE group; n = 43). For each procedure, polyps detected were described, removed, and analyzed by histology. The primary outcome was additional polyp detection rate, defined as the number of polyps detected during the second inspection divided by the total number of polyps detected during the first and the second examination.**

RESULTS: **A total of 774 polyps were detected (362 in the HD-WLE group and 412 in the HD-CE group); 54.2% were hyperplastic, 13.8% were adenomas, and 10.9% were sessile serrated polyps. There was a significantly higher additional polyp detection rate in the HD-CE group (0.39; 95% CI, 0.35–0.44) than in the HD-WLE group (0.22; 95% CI, 0.18–0.27) ($P < .001$). A higher additional rate of serrated lesions proximal to the sigmoid colon were detected in the second inspection with HD-CE (0.40; 95% CI, 0.33–0.47) than with HD-WLE (0.24; 95% CI, 0.19–0.31) ($P = .001$). Detection of adenomas and serrated lesions greater than 10 mm did not differ significantly between groups. In a multivariate logistic regression analysis, only use of HD-CE was associated independently with increased polyp detection throughout the colon.**

CONCLUSIONS: **In a randomized controlled trial, we found that panchromoendoscopy increases detection of polyps (mostly of small serrated lesions) and should be considered the standard of care in patients with SPS. Studies are needed to determine the effects of this strategy on the incidence of advanced neoplasia during long-term follow-up evaluation. ClinicalTrials.gov no: NCT03476434.**

Keywords: Sessile Serrated Adenoma; CRC; Surveillance; Advanced Endoscopy.

Abbreviations used in this paper: **CE, chromoendoscopy; CRC, colorectal cancer; HD, high-definition; HP, hyperplastic polyp; SL, serrated lesion; SPS, serrated polyposis syndrome; SSP, sessile serrated polyp; WHO, World Health Organization; WLE, white-light endoscopy.**

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Summary

SPS, characterized by multiple and/or large proximal serrated lesions, increases the risk of colorectal cancer. Chromoendoscopy increases detection of adenomas and serrated lesions in average-risk populations. International guidelines and expert groups recommend the use of chromoendoscopy for SPS patient surveillance, despite little evidence. In a randomized controlled study of patients with SPS, indigo carmine panchromoendoscopy detected 2-fold more serrated lesions than high-definition, white-light endoscopy during surveillance colonoscopy of cleared colon. Chromoendoscopy should be considered the standard of care for SPS surveillance, but studies are needed to determine the effects of this strategy on the incidence of advanced neoplasia.

What You Need to Know

Background

Serrated polyposis syndrome (SPS), characterized by multiple serrated lesions, is a risk factor for colorectal cancer. Chromoendoscopy increases detection of adenomas and serrated lesions in average-risk populations, but its usefulness in patients with SPS is unclear.

Findings

In a randomized controlled study, indigo carmine panchromoendoscopy increased detection of serrated lesions by 19.5%, compared with high-definition, white-light colonoscopy, in patients with SPS. A considerable number of adenomas (28%–32%) and serrated lesions (20%–40%) were missed during surveillance colonoscopy in these patients.

Implications for patient care

Panchromoendoscopy increases detection of polyps (mostly small polyps), but further studies are needed.

Introduction

Serrated polyposis syndrome (SPS) is the most common colorectal polyposis syndrome and is characterized by the emergence of large and/or numerous serrated lesions (SLs) throughout the colorectum.[1] SLs are classified into sessile serrated polyps (SSPs) with or without dysplasia, hyperplastic polyps (HPs), and traditional serrated adenomas.[2,3] In 2010, the World Health Organization (WHO) defined this syndrome as meeting any of the following criteria: criterion I, at least 5 SLs proximal to the sigmoid colon with 2 or more of these being 10 mm or larger in size; criterion II, any SLs proximal to the sigmoid colon in a first-degree relative with SPS; and criterion III, more than 20 SLs of any size distributed throughout the colon.[4] It has been shown that between 11.8% and 28.5% of patients with SPS present with colorectal cancer (CRC) at the time of diagnosis.[1–7] Along with the histologic progression of SLs through the serrated pathway of carcinogenesis, the increased prevalence and incidence of advanced adenomas[8] in these patients suggests that the heightened risk of CRC also is the result of a neoplastic field effect. Based on these reports, experts advise 1-year endoscopic surveillance in all patients with SPS.[9]

Tandem colonoscopy studies have shown that a significant number of polyps can be missed during conventional colonoscopy. These findings are even more evident for SLs, in which a 31% miss rate has been reported.[10] SLs often are overlooked because of their appearance: flat morphology, similar color to the surrounding mucosa, and subtle and indistinctive borders.[11] Chromoendoscopy (dye spraying onto the surface of the colon) enhances the detection of these subtle and flat polyps in the colon.[12] It has been shown that this technique increases the detection rate of SLs, overall and especially in the proximal colon, in average-risk populations.[13,14] In a multicenter randomized trial, the use of virtual chromoendoscopy (narrow-band imaging) compared with high-definition (HD) white-light colonoscopy did not show a decrease in the polyp miss rate in patients with SPS.[15]

The usefulness of dye-based chromoendoscopy in SPS patients surveillance is not well established. The primary aim of our randomized trial was to evaluate the usefulness of panchromoendoscopy with indigo carmine for the detection of colonic polyps in SPS patients, and the secondary aims were to quantify the detection of missed SLs and missed adenomas in these patients.

Patients and Methods

Study Population and Procedures

From February 2015 to July 2016, 7 centers prospectively recruited patients with SPS, aged 18 years or older, in whom clearing of all polyps was achieved previously. Polyp clearing was defined as removal of all polyps greater than 3 mm during colonoscopy and/or through a segmental colectomy when needed.[1,7,16] Exclusion criteria were as follows: known inflammatory bowel disease, hereditary CRC syndromes (ie, *APC*, *MUTYH*–biallelic, and *MMR* germline mutations), and total colectomy. To provide a more homogeneous sample, patients who were classified into the WHO criterion II also were excluded because they show a different phenotype and the increased CRC risk in this subgroup has been challenged.[15,17]

The Institutional Review Board of each participating center approved the study, and written informed consent was obtained from all patients.

All procedures were performed under moderate sedation (midazolam and/or fentanyl or pethidine) or under deep sedation with propofol at the discretion of the endoscopist. Procedures were performed with HD

systems (ie, 180/190 series in combination with EVIS EXERA II-III processors [Olympus, Tokyo, Japan]; EC 390 LI scope in combination with a Pentax processor [Pentax, Tokyo, Japan]; or 590 WL and 580 ZW endoscopes in combination with Fujinon 4400/4450 processors [Fujifilm Medical Systems, Tokyo, Japan]).

The quality of bowel cleansing was graded by each endoscopist following the Boston Bowel Preparation Scale.[18] Adequate preparation was defined as a total score of 6 or higher, with no segments of the colon scored as less than 2. Procedures in which the quality of preparation did not fulfill the requirements were excluded.

Patients were allocated in a 1:1 distribution into 1 of the 2 arms of the study by random numbers distributed from the coordinating center. After randomization, patients underwent tandem colonoscopies by the same endoscopist.

In group A, the first inspection was with HD white-light endoscopy (HD-WLE) from the cecum/ileocolonic anastomosis to the rectum, followed by a second inspection with HD-WLE. This group was called the HD-WLE group.

In group B, the first inspection was with HD-WLE from the cecum/ileocolonic anastomosis to the rectum, followed by a second inspection with pan-chromoendoscopy (HD-CE). During this procedure, the lumen was sprayed in a segmental fashion using 0.4% indigo carmine stain delivered via a specially designed dye spray catheter (Olympus PW-5V1) or via the accessory channel with a 50-mL syringe filled with indigo carmine and air. After allowing a few seconds for the dye to settle onto the mucosal surface, excess pools of indigo carmine stain were suctioned and the mucosa then was scrutinized carefully (Supplementary Figures 1 and 2). This group was called the HD-CE group.

The time to withdrawal from the cecum was measured using a stopwatch, excluding time needed for polypectomy and biopsies.

Polyps

Polyps detected during each inspection were described and then removed, except for those smaller than 4 mm, located in the distal sigmoid and the rectum, and with high confidence to be hyperplastic. Size (measured in comparison with an open biopsy forceps), morphology (using the Paris classification[17]), location, and polypectomy technique were recorded before removal. The proximal colon was defined as proximal to the sigmoid colon.

Histology was used as the gold standard. Biopsy specimens were processed and stained using standard methods, and subsequently were evaluated by experienced gastrointestinal pathologists in each center according to the Vienna criteria of gastrointestinal epithelial neoplasia.[19] Serrated lesions were assigned according to the WHO 2010 classification[4] into hyperplastic polyps, SSPs, and traditional serrated adenomas. Cytologic dysplasia among serrated polyps was analyzed both as the presence/absence of dysplasia, as well as the presence of low-grade and high-grade dysplasia. Neoplastic extension vertically into the submucosal layer or beyond was classified as invasive cancer.

Outcome Measurement

The primary outcome was the additional polyp detection rate, which was defined as the number of polyps detected during the second inspection divided by the total number of polyps detected during the first and the second examination. Polyps detected during the second examination were classified as additional detected polyps. Results were analyzed per polyp.

Advanced adenomas were defined as adenomas 10 mm or larger in size, and/or with villous histology and/or high-grade dysplasia; advanced SLs were defined as SLs that were 10 mm or larger and/or with dysplasia (including SSP with high- or low-grade dysplasia and traditional serrated adenomas). Proximal SLs were defined as those located proximal to sigmoid. Invasive CRC, advanced adenoma, and advanced SLs were grouped into advanced neoplasia.

Sample Size Calculation and Statistical Analysis

A polyp miss rate of 29% with HD-WLE was described previously in a Dutch multicenter study with SPS patients.[14] Estimating a power of 80% and a significance level of 0.05, we calculated that 516 lesions would be required to measure a difference of 15% with HD-CE. In a previous study, a median of 6 polyps was found on annual surveillance,[4] so we calculated a sample size of 86 patients for our study, 43 in each group.

Statistical analysis was performed with SPSS software version 15.0 (SPSS, Inc, Chicago, IL). Continuous variables are presented as means and SD and were compared using a Student *t* test. Categoric variables are presented as frequencies and were compared using the chi-square test. Additional polyp detection rates were compared with the chi-square test. Logistic regression analysis was used to compare polyp characteristics and polyp detection rates and was expressed as odds ratios with 95% CIs.

Results

Patients and Procedures

A total of 91 patients were enrolled in the study. A study flowchart following the Consolidated Standards of Reporting Trials guidelines is presented in Supplementary Figure 3. After the exclusion criteria were applied, 86 patients finally were randomized: 43 in the

Table 1. Baseline Demographic and Clinical Characteristics in Both Groups (n = 86)

	HD-WLE (n = 43)	HD-CE (n = 43)	*P* value
Mean age, *y*	62.9	61.5	.391
Women, n (%)	18 (41.9)	13 (30.2)	.261
SPS WHO criteria (I or I + III/III)	16/27	18/25	.659
Personal history of CRC	3 (7%)	8 (18.6%)	.106
Partial colectomy, n (%)	5 (11.6)	9 (20.9)	.243
Smoker, no/yes/previous	10/18/13	8/14/20	.334
Number of previous colonoscopies, mean	5.1	4.6	.456
Months from last colonoscopy, mean	16.5	13.6	.085
Number of previous polyps, mean			
Adenoma	5.2	4.8	.755
HP	31.6	32.5	.858
SSP	4.2	3.1	.450

CE, chromoendoscopy; CRC, colorectal cancer; HD, high-definition; HP, hyperplastic polyp; SPS, serrated polyposis syndrome; SSP, sessile serrated polyp; WHO, World Health Organization; WLE, white-light endoscopy.

HD-WLE group and 43 in the HD-CE group. Detailed demographic and clinical characteristics are shown in Table 1; there were no statistical differences in age or sex between the 2 groups. The mean examination time during the first withdrawal was similar in both groups: in the HD-WLE group it was 12.03 ± 4.06 minutes, and in the HD-CE group it was 12.79 ± 3.16 minutes ($P = .350$). Withdrawal time during the second inspection was longer in the HD-CE group: in the HD-WLE group it was 10.23 ± 3.83 minutes, and in the HD-CE group it was 14.31 ± 4.51 minutes ($P = .0001$).

Polyps

Polyps with histologically normal tissue were excluded from the analysis: 123 in the first inspection (38 in the HD-WLE group and 85 in the HD-CE group) and 84 in the second inspection (15 [28.3%] in the HD-WLE group and 69 [44.8%] in the HD-CE group).

A total of 774 polyps were included, 362 in the HD-WLE group and 412 in the HD-CE group. Morphologic and histologic polyp characteristics are shown in Table 2.

In the HD-WLE group, 282 polyps were detected during the first inspection and another 80 polyps were detected during the second inspection (57 HPs, 5 SSPs, and 18 adenomas). In the HD-CE group, 251 polyps were detected during the first inspection and another 161 polyps were detected during the second with chromoendoscopy (117 HPs, 21 SSPs, and 23 adenomas) (Table 3). Most of the polyps found during the second examination were SLs: 72.7% HPs and 13.0% SSPs in the HD-CE group vs 71.3% HPs and 6.3% SSPs in the HD-WLE group. The distribution of these SLs

Table 2. Comparison of Endoscopic Findings of HD-WLE and HD-CE

	HD-WLE (n = 43)		*P* value	HD-CE (n = 43)		*P* value
Total polyps	362			412		
Polyps size, mean	4.4 mm (SD, 2.7 mm)			4.3 mm (SD, 2.4 mm)		.278
Median (IQR)	4.0 mm (3–5 mm)			4.0 mm (3–5 mm)		
	First inspection	Second inspection		First inspection	Second inspection	
Location			.002			.068
Ascending colon	47 (16.7%)	7 (8.8%)		34 (13.5%)	17 (10.6%)	
Transverse colon	93 (33.0%)	27 (33.8%)		73 (29.1%)	41 (25.5%)	
Descending colon	40 (14.2%)	26 (32.5%)		58 (23.1%)	45 (28.0%)	
Sigmoid colon	70 (24.8%)	15 (18.8%)		64 (25.5%)	45 (28.0%)	
Rectum	32 (11.3%)	5 (6.3%)		22 (8.8%)	13 (8.1%)	
Morphology, Paris classification			.398			.001
0–Is	23 (8.2%)	6 (7.5%)		52 (20.7%)	21 (13%)	
0–Ip	0 (0%)	0 (0%)		1 (0.4%)	0 (0%)	
0–IIa	201 (71.3%)	51 (63.8%)		177 (70.5%)	104 (64.6%)	
0–IIb	57 (20.2%)	22 (27.5%)		18 (7.2%)	35 (21.7%)	
0–IIc	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
0–III	0 (0%)	0 (0%)		0 (0%)	1 (0.6%)	
Histology			.256			.067
Normal tissue	38 (11.9%)	15 (15.8%)		85 (25.3%)	69 (30.0%)	
HP	203 (63.4%)	57 (60.0%)		155 (46.1%)	117 (50.9%)	
SSP	33 (10.3%)	5 (5.3%)		48 (14.3%)	21 (9.1%)	
Adenoma LGD	46 (14.4%)	18 (18.9%)		48 (14.3%)	23 (10.0%)	
Adenoma HGD/CRC	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
No histology	6 (1.9%)	4 (4.2%)		8 (2.4%)	6 (2.6%)	

CE, chromoendoscopy; CRC, colorectal cancer; HGD, high-grade dysplasia; HP, hyperplastic polyp; IQR, interquartile range; LGD, low-grade dysplasia; SSP, sessile serrated polyp; WLE, white-light endoscopy.

Table 3. Number of Polyps in First and Second Inspections

	Group A (HD-WLE)			Group B (HD-CE)		
	Total	First inspection HD-WLE	Second inspection HD-WLE	Total	First inspection HD-WLE	Second inspection HD-CE
Polyps per patient						
Mean (SD)		6.7 (4.8)	2.5 (1.5)		6.0 (4.3)	3.8 (2.2)
Median (IQR)		6 (3–9)	2 (1–3)		5 (3–8)	3 (2–5)
Total polyps	362	282	80	412	251	161
SLs (HP + SSP)	298	236	62	341	203	138
HP	260	203	57	272	155	117
SSP	38	33	5	69	48	21
Adenomas	64	46	18	71	48	23
SLs in proximal colon	181	137	44	203	122	81
SLs >5 mm in proximal colon	72	59	13	62	39	23
SLs ≥10 mm	12	11	1	16	14	2

CE, chromoendoscopy; HD, high-definition; HP, hyperplastic polyp; IQR, interquartile range; SL, serrated lesion; SPS, serrated polyposis syndrome; SSP, sessile serrated polyp; WLE, white-light endoscopy.

throughout the colon was homogeneous; more SLs were resected in the distal colon in the HD-CE group (40.9%) than in the HD-WLE group (29%), but without statistical significance ($P = .343$) (see supplementary Table 1 for details).

No traditional serrated adenoma, advanced adenoma, or adenocarcinoma was detected. A total of 28 SLs of 10 mm or greater were resected: 11 in the first inspection on HD-WLE and only 1 in the second, and 14 in the first inspection on HD-CE and 2 in the second.

The mean size of polyps in the HD-WLE group was 4.5 ± 2.9 mm (range, 1–30 mm) in the first inspection, and 4.3 ± 1.9 mm (range, 1–10 mm) in the second. In the HD-CE group, the mean size of polyps was 4.3 ± 2.4 mm (range, 1–15 mm) in the first inspection; and 4.1 ± 2.3 mm (range, 1–20 mm) in the second.

Additional Polyp Detection Rate

A total of 241 polyps were detected during the second inspection, compared with 774 total polyps in both inspections, so the overall additional polyp detection rate was 0.31 (95% CI, 0.28–0.35). The additional polyp detection rate in the HD-CE group was higher than in the HD-WLE group: 0.39 (95% CI, 0.35–0.44) vs 0.22 (95% CI, 0.18–0.27) ($P < .001$). As shown in Table 4, the additional detection rate for SLs (HPs + SSPs) was higher in the HD-CE group compared with the HD-WLE group; this also was observed for SLs located proximal to the sigmoid and SLs greater than 5 mm, whereas it did not reach statistical significance for adenomas and for SSPs.

The associations between SPS patient phenotype, polyp characteristics, the use of chromoendoscopy, and additional polyp detection rates are shown in Table 5. The additional detection rate for flat polyps (0–II) was higher than for sessile polyps (0–Is): 0.39 vs 0.27; and also for polyps smaller than 10 mm compared with polyps 10 mm or greater: 0.39 vs 0.18; in both cases the difference did not reach statistical significance ($P = .086$ and $P = .061$, respectively). There were no differences in either additional detection rates for the proximal or distal location of polyps, or between the histology for adenomas or SLs, or between the different SPS phenotypes. In the multivariable analysis, only the use of chromoendoscopy in the

Table 4. Additional Polyp Detection Rates Risk Difference: HD-WLE and HD-CE

	Additional polyp detection rate HD-WLE (95% CI)	Additional polyp detection rate HD-CE (95% CI)	Additional polyp detection rate risk difference	*P* value
All polyps	0.22 (0.18–0.27)	0.39 (0.34–0.44)	0.17	<.001
SLs	0.21(0.17–0.26)	0.40 (0.35–0.46)	0.19	<.001
SSPs	0.13 (0.06–0.27)	0.29 (0.20–0.41)	0.16	.059
SLs in proximal colon	0.24 (0.19–0.31)	0.40 (0.33–0.47)	0.16	.001
SLs >5 mm[a]	0.18 (0.11–0.29)	0.37 (0.26–0.48)	0.19	.013
Adenomas	0.28 (0.19–0.40)	0.32 (0.23–0.44)	0.04	.590
Lesions ≥10 mm	0.15 (0.04–0.42)	0.23 (0.10–0.43)	0.08	.599

CE, chromoendoscopy; HD, high-definition; SL, serrated lesion; SSP, sessile serrated polyp; WLE, white-light endoscopy.
[a]In proximal colon.

Table 5. Additional Polyp Detection Rate Association With Polyp Characteristics, SPS Criteria, and the Use of Chromoendoscopy

	N	Additional polyp	Additional polyp rate	Univariate, OR (95% CI)	*P*	Multivariate, OR (95% CI)	*P*
Histology							
Adenomatous	135	41	0.30	0.96 (0.64–1.43)	.832	0.99 (0.64–1.53)	.974
Serrated	639	200	0.31				
Morphology							
Flat	672	214	0.32	0.77 (0.42–1.23)	.275	0.64 (0.39–1.05)	.079
Sessile	102	27	0.27				
Size							
<10 mm	740	235	0.32	0.46 (0.19–1.13)	.082	0.44 (0.18–1.09)	.079
≥10 mm	34	6	0.18				
Location							
Proximal	508	163	0.32	0.88 (0.64–1.21)	.430	0.84 (0.59–1.17)	.299
Distal	266	78	0.29				
Group							
HR-WL	362	80	0.22	2.26 (1.65–3.12)	<.001	2.49 (1.79–3.47)	<.001
HR-CE	412	161	0.39				
SPS criteria							
I or I + III	264	81	0.31	1.03 (0.75–1.42)	.844	1.20 (0.86–1.68)	.291
III	510	160	0.31				

CE, chromoendoscopy; OR, odds ratio; SPS, serrated polyposis syndrome; WLE, white-light endoscopy.

second inspection was associated with an increase in polyp detection in comparison with white light (odds ratio, 2.41; 95% CI, 1.74–3.32) (Table 5).

After exclusion of patients with prior colectomy and/or personal history of CRC, similar results were found (Supplementary Tables 2–6).

Missed Polyps

A total of 41 adenomas were missed after the first inspection (18 in group A and 23 in group B), thus the overall adenoma miss rate was 30.4%. In case of SLs, 200 SLs (HP and SSP) were missed after the first inspection (62 in group A and 138 in group B), for an overall SL miss rate of 31.3% for both groups.

Discussion

In this randomized, multicenter study, we showed that indigo carmine panchromoendoscopy improves the detection of polyps in SPS patients. Chromoendoscopy detected 2-fold more SLs than conventional WLE during surveillance colonoscopy of a previously cleared colon in SPS patients.

This study evaluated the usefulness of dye-based chromoendoscopy in the surveillance of SPS patients. The role of electronic chromoendoscopy in SPS has been evaluated before in 2 randomized cross-over studies performed by the same Dutch group and showed conflicting results: the first was a single-center study that included 22 patients and showed that narrow-band imaging was associated with a lower polyp miss rate than high-resolution WLE (10% vs 36%; $P < .001$)[20]; the second was a multicenter study including 52 SPS patients and did not corroborate the previous results (20% vs 29%; $P = .065$).[15] The investigators justified these conflicting findings by the fact that the first pilot study was performed by a single endoscopist, at a single institution, and with older endoscopic equipment.

Despite this scarce and inconsistent evidence, the guidelines of the European Society of Gastrointestinal Endoscopy strongly recommend the use of pancolonic virtual or conventional chromoendoscopy for SPS patients (low-quality evidence, strong recommendation).[21] This recommendation is based on the fact that SLs are easily overlooked and that there is strong evidence that chromoendoscopy increases the detection of SLs in the general population.[3] However, there are no data that specifically address the usefulness of panchromoendoscopy for the surveillance of this high-risk group.

Our results show that a second look with chromoendoscopy detected 39% additional polyps in comparison with 22% detected with white-light. The number of additional detected adenomas and additional detected polyps that were 10 mm or larger were similar in both groups of the study; however, HD-CE detected significantly more SLs than HD-WLE. As expected, chromoendoscopy was especially useful to detect flat and subtle polyps, such as small SLs, and added little value for the detection of adenomas (usually darker than surrounding mucosa) and large polyps. The clinical significance of these finding may be challenged because the role of small SLs in colorectal carcinogenesis is dubious. Nevertheless, consensus expert panels have recommended the removal of all SLs proximal to the sigmoid and those larger than 5 mm in the rectum and sigmoid in the general population[8] because of their association with advanced neoplasia during surveillance.[22] In addition,

previous data have shown invasive carcinoma in diminutive SLs during SPS surveillance suggesting that, in this specific scenario, even small SLs (<10 mm) have to be taken into consideration and removed.[5,7] The role of SSP as a precursor lesion for CRC is more widely accepted. In our study, the additional detection rate for SSP was higher in the HD-CE group (0.29 in HD-CE vs 0.13 in HD-WL; $P = .059$), but this was not statistically significant, probably owing to an insufficient sample size. Moreover, it is well known that there is poor interobserver agreement in the histopathologic classification of SLs,[23] leading to misclassification of small SSPs into hyperplastic polyps. As has been performed previously in several studies on SLs and SPS, we decided to mitigate this possible bias by considering SLs, as a whole and regardless of their specific subtype, as our main outcome.[5–9,15,17] It should be noted that although approximately 70% of additional SLs detected by chromoendoscopy were HPs, at least two-thirds were located proximal to the sigmoid colon, underscoring the clinical significance of this finding in SPS.

The low prevalence of advanced neoplasia in our cohort may be explained by the fact that all patients were on a standardized surveillance program and had undergone several previous colonoscopies (mean, 5.1 for the HD-WLE group; mean, 4.6 for the HD-CE group), with a mean of 16.5 and 13.6 months, respectively, from the last colonoscopy. It should be noted that we still detected 28 SLs of 10 mm or greater, most of them on first inspection, and one 20-mm SL in the second inspection with CE.

Interestingly, despite high-definition endoscopes, highly motivated endoscopists, and the context of a trial, the number of missed polyps, including adenomas, was considerable in both arms of the study: the adenoma miss rate was 28% in the HD-WLE group and 32% in the HD-CE group. This finding is in accordance with previous back-to-back video colonoscopy studies[10] and shows that despite "ideal" conditions, polyps still are overlooked.

Our study was limited by performance bias because both inspections were performed by the same endoscopist who was not blinded to the technique. However, the tandem design allowed assessing the effect of chromoendoscopy, avoiding the second-look effect. Withdrawal time during the second inspection with chromoendoscopy was longer than during white-light, mainly because of the extra time used to introduce the spray catheter through the channel, spread the dye, and remove the excess. However, we cannot rule out that this longer withdrawal time also partially could have contributed to the higher detection rates in the chromoendoscopy arm.

Another point to note is that the number of polyps with normal histology detected in the second inspection with chromoendoscopy was significantly higher in the HD-CE group (69 of 230; 30.0%) in contrast to the HD-WLE group (15 of 95; 15.8%). The application of indigo carmine may allow detecting more elevated areas of mucosa suspected of being neoplastic lesions. The increase in the detection of polyps with normal histology leads to an increase in examination time, possible adverse events related to polypectomy, increased workload for pathologists, and likely an unnecessary expenditure of resources. Nevertheless, it is important to point out that more than 35% of the false-positive samples were obtained by a single investigator. However, excluding the cases performed by this examiner did not significantly impact the results (Supplementary Tables 7–9). Consequently, this undesirable effect of chromoendoscopy may be not reproducible in other settings.

Despite our positive results, we are aware that most clinicians will not be motivated to use such a cumbersome technique to find additional small serrated lesions, especially in patients who are undergoing frequent surveillance anyway. SPS is the most frequent polyposis syndrome[1] and represents a significant workload for endoscopy units worldwide. At this time, most clinical guidelines recommend annual colonoscopies in SPS patients, but this recommendation is not based on robust evidence. In fact, recent longitudinal data from the Dutch and Spanish SPS cohorts have shown that although the incidence of CRC during appropriate surveillance is very low (1.4% and 2.6%, respectively),[5,7] up to 42% (95% CI, 32.4–51.7) of patients will develop advanced neoplasia within 3 years.[19] The risk of advanced neoplasia during follow-up evaluation differs according to certain predictors at the moment of diagnosis (ie, patients who fulfill type I + III WHO criteria are at higher risk).[5,7,19] Consequently, it has been suggested that surveillance intervals should be personalized according to SPS phenotype. Interestingly, we have found that the benefit of chromoendoscopy was independent of the patients' phenotype. In future studies, the increase in polyp detection offered by chromoendoscopy may be used to better adjust surveillance intervals and optimize the use of endoscopic resources. Overall, taking into consideration that chromoendoscopy is a technique that does not require expensive equipment,[24] we recommend the use of panchromoendoscopy as the standard of care for SPS surveillance.

In conclusion, our study shows that panchromoendoscopy allows increased polyp detection compared with white-light colonoscopy in the surveillance of SPS patients. The increase in polyp detection is mostly for small lesions with questionable oncogenic potential, and the clinical impact of this finding needs to be elucidated. Specifically, the effect of chromoendoscopy-based surveillance on the incidence of advanced neoplasia during follow-up evaluation, and whether it allows lengthening of surveillance intervals for certain SPS patients should be addressed in future studies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical*

Gastroenterology and Hepatology at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.10.029.

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Conflicts of interest
This authors discloses the following: Maria Pellisé has been a consultant for Norgine, Iberia until 2017, has received fees for conferences from Norgine, Olympus, and CasenRecordati, and receives an editorial fee from Thieme. The remaining authors disclose no conflicts.

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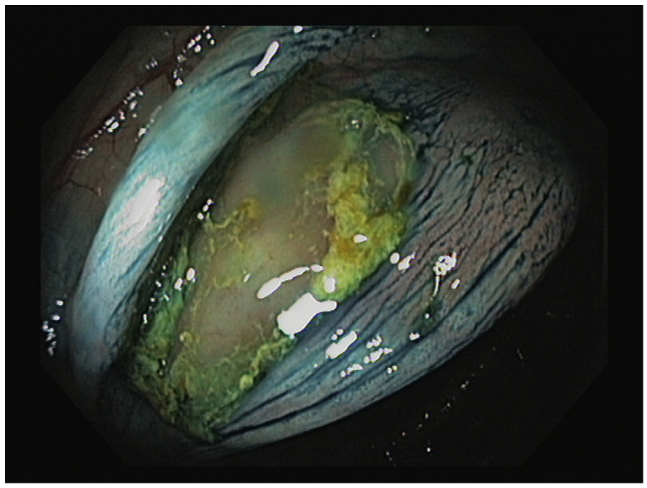
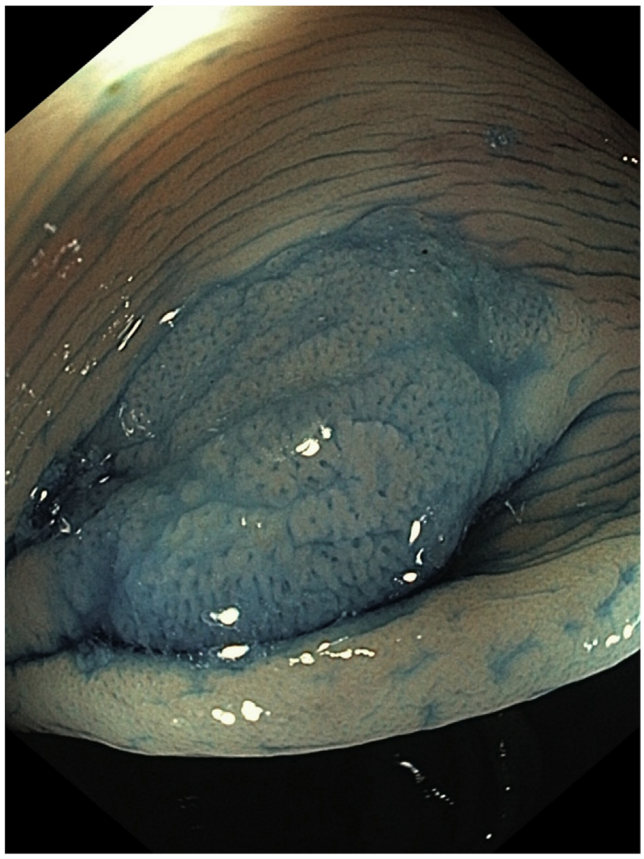
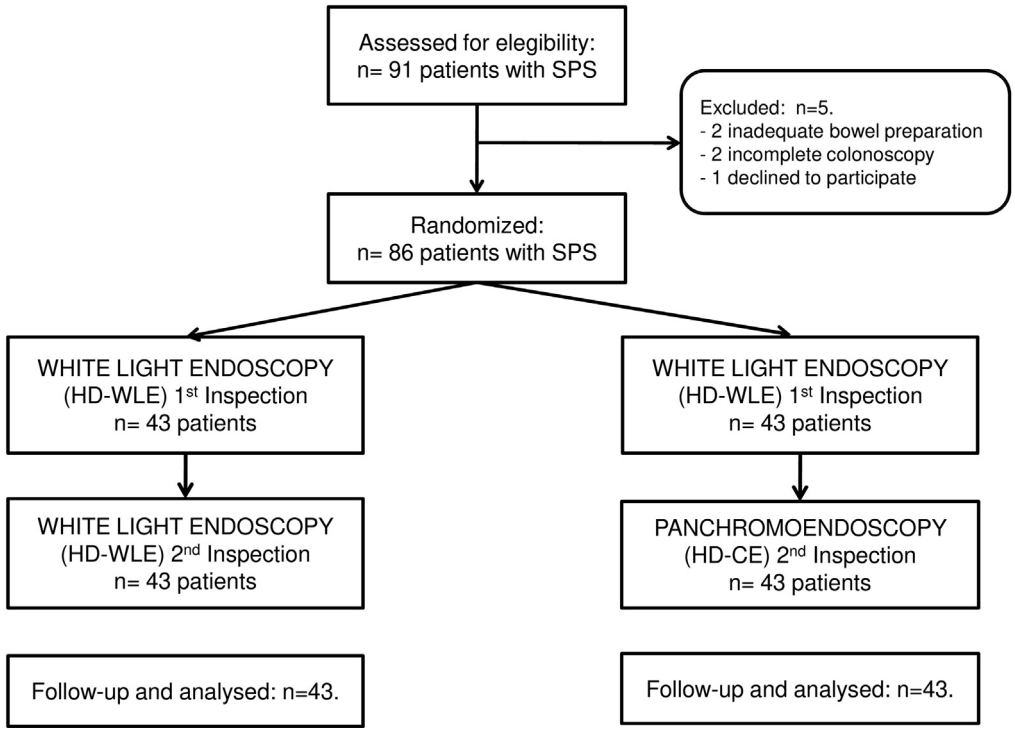


Supplementary Figure 1. A typical flat-elevated (Paris 0–IIa) polyp with a mucous cap corresponding to a SSP. The mucous cap prevents staining on the polyp surface per se. However, it permits stain to highlight the borders of the lesion.



Supplementary Figure 2. This flat (Paris 0–IIb) polyp with irregular borders also is covered by a mucous cap. The colon is very clean and there is no fecal debris. In this instance, indigo carmine stains the surface of the polyp and nicely highlights a Kudo pit pattern type II (or II–0), which is characteristic of serrated lesions.



Supplementary Figure 3. Study flow chart.

Supplementary Table 1. Distribution of Serrated Lesions in First and Second Inspection, Excluding Patients With Prior Colectomy and/or Personal History of CRC

	Polyps, polyps/total, %			
	Group A (HD-WLE)		Group B (HD-CE)	
	First inspection HD-WLE	Second inspection HD-WLE	First inspection HD-WLE	Second inspection HD-CE
Ascending colon	23, 9.7	2, 3.2	14, 6.9	7, 5.1
Transverse colon	75, 31.8	19, 30.6	62, 30.5	34, 24.8
Descending colon	39, 16.5	23, 37.1	46, 22.7	40, 29.2
Sigmoid colon and rectum	99, 41.9	18, 29	81, 39.9	57, 40.9
Total	236	62	203	138

Supplementary Table 2. Baseline Demographic and Clinical Characteristics in Both Groups (n = 72), Excluding Patients With Prior Colectomy and/or a Personal History of CRC

	HD-WLE (n = 38)	HD-CE (n = 34)	*P* value
Mean age, *y*	63.2	59.9	.074
Women, n (%)	16 (42.1)	12 (35.3)	.350
SPS WHO criteria, I or I + III/III	12/26	13/21	.351
Smoker, no/yes/previous	8/16/12	7/13/13	.287
Number of previous colonoscopies, mean	4.6	4.4	.711
Months from last colonoscopy, mean	16.9	13.4	.058
Number of previous polyps, mean			
Adenoma	4.7	4.4	.828
HP	29.9	33.1	.521
SSP	3.9	3.1	.632
Mean time of first inspection, *min*	12.2	12.7	.610
Mean time of second inspection, *min*	10.6	14.2	.001

Supplementary Table 3. Comparison of Endoscopic Findings of HD-WLE and HD-CE, Excluding Patients With Prior Colectomy and/or a Personal History of CRC

	HD-WLE (n = 38)	HD-CE (n = 34)	*P* value
Total polyps	338	320	
Polyps size, mean	4.5 mm (SD, 2.8)	4.15 mm (SD, 2.2)	.102
Median (IQR), *mm*	4.0 (3–5)	4.0 (3–5)	
Location, n (%)			
Ascending colon	53 (16)	44 (14)	.146
Transverse colon	109 (32)	79 (25)	
Descending colon	60 (18)	72 (23)	
Sigmoid colon	81 (24)	91 (28)	
Rectum	35 (10)	34 (10)	
Morphology, Paris classification, n (%)			
0-Is	22 (6.5)	55 (17.2)	.001
0-Ip	0 (0)	1 (0.2)	
0-IIa	242 (71.6)	227 (70.9)	
0-IIb	74 (21.9)	36 (11.3)	
0-IIc	0 (0)	0 (0)	
0-III	0 (0)	1 (0.2)	
Histology, n (%)			
Normal tissue	52 (13.3)	124 (27.9)	.001
HP	249 (63.7)	210 (47.3)	
SSP	33 (8.4)	56 (12.6)	
Adenoma LGD	57 (14.6)	54 (12.2)	
Adenoma HGD/CRC	0	0	
No histology	10 (2.3)	14 (2.4)	

HGD, high-grade dysplasia; IQR, interquartile range; LGD, low-grade dysplasia.

Supplementary Table 4. Number of Polyps in First and Second Inspection, Excluding Patients With Prior Colectomy and/or Personal History of CRC

	Group A (HD-WLE)			Group B (HD-CE)		
	Total	First inspection HD-WLE	Second inspection HD-WLE	Total	First inspection HD-WLE	Second inspection HD-CE
Number of polyps per patient						
Mean (SD)		6.7 (4.8)	2.5 (1.5)		6.0 (4.3)	3.8 (2.2)
Median (IQR)		6 (3–9)	2 (1–3)		5 (3–8)	3 (2–5)
Total polyps	338	265	73	320	192	128
SLs, HP + SSP	281	225	56	266	156	110
HPs	248	196	52	210	115	95
SSPs	33	29	4	56	41	15
Adenomas	57	40	17	54	36	18
SLs in proximal colon	169	129	40	146	81	65
SLs > mm in proximal colon	41	35	6	34	19	15
SLs ≥10 mm	12	10	2	12	10	2

IQR, interquartile range.

Supplementary Table 5. Additional Polyp Detection Rates Risk Difference: HD-WLE and HD-CE, Excluding Patients With Prior Colectomy and/or a Personal History of CRC

	Additional polyp detection rate HD-WLE, % (95% CI)	Additional polyp detection rate HD-CE, % (95% CI)	Additional polyp detection rate risk difference, %	*P* value
All polyps	21.6 (17.5–26.3)	40.0 (34.8–45.5)	18.4	<.001
SLs	19.9 (15.7–24.9)	41.4 (35.6–47.4)	21.5	<.001
SSPs	12.1 (4.8–27.3)	26.8 (16.9–39.6)	14.7	.103
SLs in proximal colon	23.7 (17.9–30.6)	44.5 (36.7–52.6)	20.8	<.001
SLs >5 mm[a]	14.6 (6.9–28.4)	44.1 (28.9–60.5)	29.5	.0046
Adenomas	29.8 (19.5–42.7)	33.3 (22.2–46.6)	3.5	.691
Lesions ≥10 mm	16.7 (4.7–44.8)	16.7 (4.7–44.8)	0.0	1.00

[a]In proximal colon.

Supplementary Table 6. Additional Polyp Detection Rate Association With Polyp Characteristics and the Use of Chromoendoscopy, Excluding Patients With Prior Colectomy and/or a Personal History of CRC

	N	Additional polyp	Additional polyp rate, %	Univariate, OR (95% CI)	*P*	Multivariate, OR (95% CI)	*P*
Histology							
Adenomatous	111	35	31.5	1.06 (0.68–1.64)	.805	0.94 (0.58–1.52)	.938
Serrated	547	166	30.3				
Morphology							
Flat	581	176	30.3	0.90 (0.54–1.50)	.697	0.87 (0.51–1.50)	.620
Sessile	77	25	32.5				
Size							
<10 mm	634	197	31.1	0.44 (0.15–1.32)	.133	0.39 (0.13–1.20)	.101
≥10 mm	24	4	16.7				
Location							
Proximal	417	137	32.9	0.74 (0.52–1.05)	.091	0.67 (0.46–0.98)	.037
Distal	241	64	26.6				
Group							
HR-WL	338	73	21.6	2.42 (1.72–3.41)	<.001	2.54 (1.79–3.59)	<.001
HR-CE	320	128	40.0				

NOTE. The unique meaningful difference was found in the multivariable analysis in which the proximal polyp location (OR, 0.67; 95% CI, 0.46–0.98) appeared as an independent factor associated with an increase in polyp detection in addition to the use of chromoendoscopy (OR, 2.54; 95% CI, 1.79–3.59).

Supplementary Table 7. Comparison of Endoscopic Findings of HD-WLE and HD-CE, Excluding Cases Performed by 1 Specific Examiner

	HD-WLE (n = 27)	HD-CE (n = 35)	*P* value
Total polyps	193	339	
Polyp size, mean, *mm*	4.26 (SD, 3.2)	4.46 (SD, 2.5)	.443
Median (IQR), *mm*	3.0 (3–5)	4.0 (3–5)	
Location, n (%)			
Ascending colon	27 (14)	46 (13.6)	.069
Transverse colon	69 (35.8)	92 (27.1)	
Descending colon	40 (20.7)	92 (27.1)	
Sigmoid colon	35 (18.1)	82 (24.2)	
Rectum	22 (11.4)	22 (8.0)	
Morphology, Paris classification, n (%)			
0-Is	27 (14.0)	73 (21.5)	.018
0-Ip	0 (0)	1 (0.3)	
0-IIa	121 (62.7)	220 (64.9)	
0-IIb	43 (22.3)	42 (12.4)	
0-IIc	0 (0)	0 (0)	
0-III	0 (0)	0 (0)	
Histology, n (%)			
Normal tissue	27 (12.3)	94 (21.7)	.008
HP	129 (58.6)	209 (48.3)	
SSP	25 (11.4)	69 (15.9)	
Adenoma LGD	39 (17.7)	61 (14.1)	
Adenoma HGD/CRC	0	0	
No histology	7	12	

HGD, high-grade dysplasia; IQR, interquartile range; LGD, low-grade dysplasia.

Supplementary Table 8. Additional Polyp Detection Rates Risk Difference: HD-WLE and HD-CE, Excluding Cases Performed by 1 Specific Examiner

	Additional polyp detection rate HD-WLE (95% CI)	Additional polyp detection rate HD-CE (95% CI)	Additional polyp detection rate risk difference	*P* value
All polyps	0.23 (0.17–0.29)	0.37 (0.32–0.42)	0.14	.001
SLs	0.20 (0.15–0.27)	0.39 (0.34–0.45)	0.19	<.001
SSPs	0.16 (0.06–0.35)	0.29 (0.20–0.41)	0.13	.190
SLs in proximal colon	0.25 (0.17–0.34)	0.41 (0.34–0.48)	0.16	.007
SLs >5 mm[a]	0.20 (0.08–0.42)	0.41 (0.27–0.56)	0.21	.111
Adenomas	0.33 (0.21–0.49)	0.28 (0.18–0.40)	-0.05	.691
Lesions ≥10 mm	0.13 (0.02–0.47)	0.19 (0.07–0.40)	0.06	.676

[a]In proximal colon.

Supplementary Table 9. Additional Polyp Detection Rate Association With Polyp Characteristics and the Use of Chromoendoscopy, Excluding Cases Performed by 1 Specific Examiner

	N	Additional polyp	Additional polyp rate	Univariate, OR (95% CI)	*P*	Multivariate, OR (95% CI)	*P*
Histology							
Adenomatous	100	30	0.30	0.89 (0.56–1.43)	.642	0.92 (0.56–1.52)	.746
Serrated	432	140	0.32				
Morphology							
Flat	432	144	0.33	0.70 (0.43–1.15)	.156	0.66 (0.39–1.10)	.110
Sessile	100	26	0.26				
Size							
<10 mm	503	165	0.33	0.43 (0.16–1.14)	.081	0.38 (0.14–1.02)	.053
≥10 mm	29	5	0.17				
Location							
Proximal	366	123	0.34	0.78 (0.52–1.17)	.225	0.71 (0.47–1.08)	.108
Distal	166	47	0.28				
Group							
HR-WL	194	44	0.23	2.01 (1.34–2.99)	.001	2.14 (1.42–3.22)	<.001
HR-CE	339	126	0.37				