

Reassessment colonoscopy to diagnose serrated polyposis syndrome in a colorectal cancer screening population

Authors

Liseth Rivero-Sanchez^{1,2}, Maria Lopez-Ceron¹, Sabela Carballal¹, Leticia Moreira¹, Xavier Bessa³, Anna Serradesanferm⁴, Angels Pozo⁴, Josep Maria Augé⁵, Teresa Ocaña¹, Ariadna Sánchez¹, María Liz Leoz¹, Míriam Cuatrecasas⁶, Jaume Grau⁴, Josep Llach¹, Antoni Castells¹, Francesc Balaguer^{1,*}, Maria Pellisé^{1,*}

Institutions

- 1 Department of Gastroenterology, Hospital Clínic de Barcelona; and Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBEREHD), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain
- 2 Fundació Clínic per a la Recerca Biomèdica (FCRB), Barcelona, Spain
- 3 Department of Gastroenterology, Hospital del Mar, Barcelona, Spain
- 4 Preventive Medicine and Hospital Epidemiology Department, Hospital Clínic de Barcelona, Barcelona, Spain
- 5 Biochemistry Department, Hospital Clínic de Barcelona, Barcelona, Spain
- 6 Pathology Department, Hospital Clínic de Barcelona, Barcelona, Spain

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Bibliography

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Corresponding author

Maria Pellisé Urquiza, MD PhD, Department of Gastroenterology, Hospital Clínic of Barcelona, Villarroel 170, 08036 Barcelona, Spain, mpellise@clinic.ub.es

ABSTRACT

Background and study aims Serrated polyposis syndrome (SPS) is a high risk condition for colorectal cancer (CRC). Surveillance strategies for patients with serrated lesions remain controversial. We aimed to evaluate a diagnostic strategy to detect SPS consistently during reassessment colonoscopy in patients with proximal serrated lesions.

Methods This was a retrospective study of all individuals from a fecal immunochemical test (FIT)-based CRC screening program (2010–2013) with one or more serrated lesions of ≥ 5 mm proximal to the sigmoid colon on baseline colonoscopy. We analyzed all individuals empirically scheduled for a reassessment colonoscopy aimed at diagnosing SPS within 1 year. Reassessment colonoscopy was performed with standard white-light or chromoendoscopy \pm high definition endoscopy depending on availability. SPS diagnosis was based on the cumulative number of polyps in both the baseline and reassessment colonoscopies. Factors associated with SPS diagnosis were analyzed.

Results From 3444 screening colonoscopies, 196 patients met the study entry criteria, of whom 11 patients (0.32%) met the criteria for SPS on baseline colonoscopy. Reassessment colonoscopies were performed in 71 patients at 11.9 ± 1.7 months and detected 20 additional patients with SPS, a tripling of the rate of SPS up to 0.90%. Independent factors associated with SPS diagnosis were: having five or more proximal serrated lesions (odds ratio [OR] 4.01 [95% confidence interval 1.20–13.45]; $P=0.02$) or two or more sessile serrated polyps ≥ 10 mm (OR 6.35 [1.40–28.81]; $P=0.02$) on baseline colonoscopy and the use of chromoendoscopy \pm high definition endoscopy during reassessment colonoscopy (OR 4.99 [1.11–22.36]; $P=0.04$).

Conclusions A 1-year reassessment colonoscopy using chromoendoscopy and high definition endoscopes substantially improves SPS detection in individuals from a FIT-based screening program with proximal serrated lesions. Five or more proximal serrated lesions or two or more sessile serrated polyps ≥ 10 mm could be thresholds for requiring a reassessment colonoscopy. Prospective studies are required to validate these results and adjust surveillance recommendations in patients with serrated lesions.

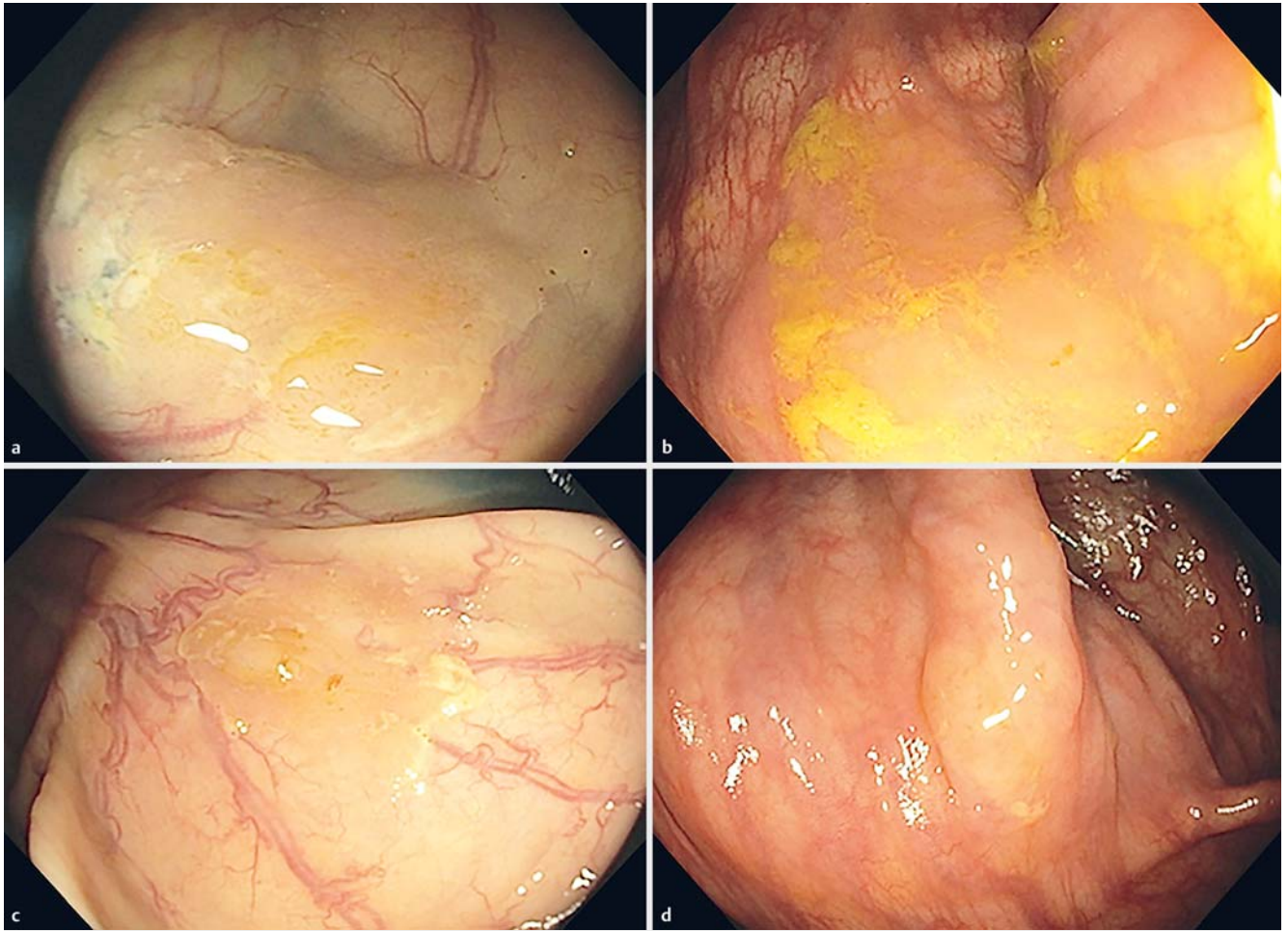
Introduction

Serrated polyposis syndrome (SPS) is a heterogeneous disease arbitrarily defined according to the following World Health Organization (WHO) criteria [1]: (i) at least five serrated lesions proximal to the sigmoid colon, with two or more of them being ≥ 10 mm in diameter; (ii) at least one serrated lesion proximal to the sigmoid colon in a patient with a first-degree relative with SPS; or (iii) >20 serrated lesions spread throughout the colon. SPS prevalence has been reported as between 0.34% and 0.66%

of the population in the context of screening programs based on fecal occult blood testing (FOBT) [2, 3]. In establishing a diagnosis of SPS, the number of polyps is cumulative, so it is often established after successive procedures [1]. A study showed that up to 45% of SPS patients are not diagnosed at first colonoscopy, even if this is performed by an experienced endoscopist [4].

The presence of numerous or large serrated lesions (► Fig. 1) is a common finding in a fecal immunochemical test (FIT)-based colorectal cancer (CRC) screening program [5]. However, surveillance recommendations for patients with serrated lesions remain controversial. The American Gastroenterology As-

* These authors share senior authorship.



► **Fig. 1** Examples of sessile serrated adenomas/polyps (SSA/Ps) showing their typical flat morphology, color that is similar to the surrounding mucosa, mucus cap, and subtle borders.

sociation (AGA) recommends follow-up intervals that range from 3 to 10 years, according to location, size, dysplastic component, and histological subtype of any serrated lesions, but annually if one of the WHO criteria of SPS is fulfilled [6]. The European Society of Gastrointestinal Endoscopy (ESGE) proposes a simple approach that takes into account size and dysplastic component [7]. An expert panel has recommended a 3-year surveillance colonoscopy in patients with at least one sessile serrated adenoma/polyp (SSA/P) or traditional serrated adenoma (TSA) ≥ 10 mm, three or more SSA/Ps or TSAs of any size, or any number of SSA/Ps with dysplasia [8]. However, the diagnostic yield of surveillance colonoscopy in these patients remains poorly studied.

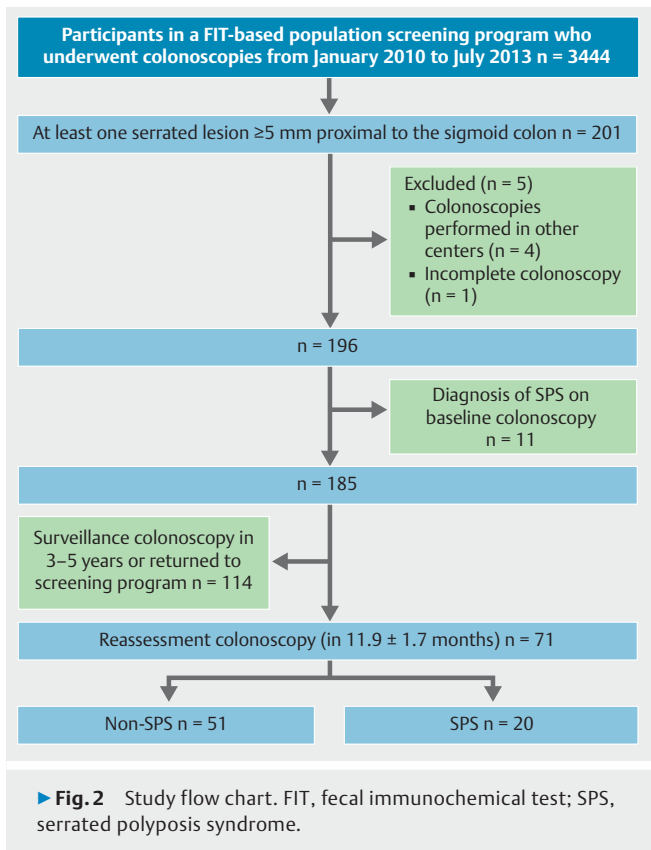
We hypothesized that, in a FIT-based population screening program, a reassessment colonoscopy in patients with proximal serrated lesions would detect missed SPS patients. Accordingly, our aims were to assess the incremental rate of SPS diagnosis after a reassessment colonoscopy in patients with proximal serrated lesions on their baseline colonoscopy and, secondly, to identify factors predictive of a diagnosis of SPS.

Methods

Patients and study design

This was a retrospective study of prospectively collected data from the organized Barcelona FIT-based CRC screening program. This program, which began in 2010, is based on a biennial FIT (OC-Sensor; Eiken, Japan; cut-off ≥ 20 μg of hemoglobin/mg of feces) in asymptomatic individuals aged 50–69 years. All colonoscopies and pathology reports are reviewed weekly by a committee composed of expert gastroenterologists, endoscopists, and nurses before follow-up recommendations are given. Until 2015, post-polypectomy surveillance recommendations were based on the guidelines of the Spanish Association of Gastroenterology [9] and AGA [6]: 3-year interval for patients with “high risk adenoma” (≥ 3 adenomas or any adenoma ≥ 10 mm in size, villous histology, or high grade dysplasia); and 5-year interval for those with “low-risk adenoma” (1–2 tubular adenomas < 10 mm with low grade dysplasia).

Given the lack of surveillance recommendations for serrated lesions, patients with a significant burden of serrated lesions on their baseline colonoscopy were scheduled for a reassessment colonoscopy with the aim of potentially detecting previously



unnoticed serrated lesions. The decision to perform the reassessment colonoscopy was not standardized and was based on the presence of large or proximal serrated polyps, the presence of dysplasia, or SSA/P histology. In order to avoid selection bias, we included in the study all participants in the screening program who underwent a colonoscopy from January 2010 to July 2013, focusing the analysis on those who had presented at least one serrated lesion that was proximal to the sigmoid colon and larger than 5 mm.

When several baseline colonoscopies were needed, for example for inadequate bowel preparation, high burden of polyps, or complex polypectomy, the baseline colonoscopy was based on the date of the last colonoscopy that completely scrutinized the entire colon and/or achieved a clear colon. For analysis purposes, the findings of any repeated colonoscopies were compiled into one. Individuals who underwent baseline colonoscopy in other centers or who had an incomplete procedure (i. e. without cecal intubation) were excluded.

Data was obtained from the screening program database and from Hospital Clinic's digital medical records.

This study was approved by the Ethics and Clinical Investigation Committee from Hospital Clinic of Barcelona.

Procedures and endoscopic equipment

Baseline colonoscopies were performed following quality standards [10] by 12 experienced endoscopists, each having performed more than 400 colonoscopies per year and with a high adenoma detection rate (i. e. 29.8% in primary colonoscopy screening and 47.1% in FIT-based screening) [11–13]. Reas-

essment colonoscopies were performed by a subgroup of five of these endoscopists. The endoscopists who performed the reassessment colonoscopies had a similar adenoma detection rate to those who performed only baseline colonoscopies (48.7% vs. 46.2%; $P=0.67$).

Baseline colonoscopies were performed with standard definition white-light endoscopes (CF-Q160L/CF-Q165L in combination with an EVIS EXERA II processor; Olympus, Tokyo, Japan). According to availability, reassessment colonoscopies were performed with standard definition or high definition technology (CF-H180AL/CF-HQ190L combined with EVIS EXERA III processor; Olympus) with or without the addition of chromoendoscopy, either conventional (indigo carmine 0.4% spraying during continuous extubation) or electronic (narrow-band imaging [NBI]).

All patients were encouraged to follow a low-fiber/low-fat diet for 3 days before the procedure. Bowel cleansing was carried out with 4L of polyethylene glycol and electrolyte lavage solution (Solución Evacuante BOHM; Laboratorios Bohm S.A., Fuenlabrada, Madrid, Spain) in split doses. Bowel cleansing was considered adequate (excellent or good) if the Boston score was ≥ 6 points (≥ 2 per colonic segment).

Procedures were performed with the patients breathing spontaneously under deep sedation (propofol and remifentanyl infusion) that was administered by trained nurses supervised by anesthesiologists. Colonoscopies were scheduled in time slots of 40 minutes.

Polyp location was divided into four colonic segments: right colon (cecum, ascending colon, and hepatic flexure); transverse colon (including splenic flexure); descending colon; and sigmoid colon and rectum.

Histopathology

Polyp histology was evaluated by four expert pathologists dedicated to gastrointestinal oncology following the European guidelines for quality assurance in CRC screening and diagnosis [14]. The number, size, and histology of all lesions were registered. Serrated lesions included SSA/Ps (with or without dysplasia), hyperplastic polyps, and TSAs. Advanced adenomas were those with a villous component, size ≥ 10 mm, or high grade dysplasia (including intramucosal carcinoma). The surgical specimen was used to provide the final pathological diagnosis in patients who were treated by surgery. All lesions detected at reassessment colonoscopy were considered to have been missed at baseline colonoscopy.

Outcome measures

The primary outcome was to evaluate the rate of SPS diagnosis on baseline and reassessment colonoscopies. The rate of SPS was defined as the proportion of SPS cases diagnosed compared with the total number of patients in the screening cohort. The diagnosis of SPS on reassessment colonoscopy was made according to the cumulative number of serrated lesions detected in both colonoscopies. Secondary outcomes were to identify clinical, histopathological, and endoscopic factors that were predictive of SPS on reassessment colonoscopy using a univariable and multivariable approach.

► Table 1 Demographic characteristics and main baseline findings in patients who underwent reassessment colonoscopy and those scheduled for standard surveillance.

	Reassessment colonoscopy (n=71)	Standard surveillance (n=114)	P value (95%CI)
Patient demographics			
Mean age ± standard deviation, years	59.4 ± 5.1	58.8 ± 1.9	0.63
Sex, male, n (%)	35 (49.3%)	69 (60.5%)	0.13
Baseline findings at screening colonoscopy			
Prevalence of polyp subtype, n (%)			
Hyperplastic polyps ≥ 10 mm	18 (25.4)	34 (29.8)	0.51
Proximal hyperplastic polyps ≥ 10 mm	10 (14.1)	10 (8.8)	0.26
SSA/Ps	43 (60.6)	27 (23.7)	<0.001
SSA/Ps ≥ 5 mm	44 (62.0)	33 (28.9)	<0.001
SSA/Ps ≥ 10 mm	21 (29.6)	17 (14.9)	0.02
Proximal ¹ SSA/Ps	41 (57.7)	26 (22.8)	<0.001
Proximal ¹ SSA/Ps ≥ 10 mm	15 (21.1)	10 (8.8)	0.02
SSA/Ps with dysplasia	8 (11.2)	10 (8.8)	0.58
Adenomas	56 (78.9)	79 (69.3)	0.15
Advanced adenomas ²	42 (59.2)	44 (38.6)	0.006
Number of polyps per patient, median (IQR)			
Total serrated lesions	3 (2–6)	1 (1–2)	<0.001
Adenomas	2 (1–5)	1 (0–2)	<0.001
Advanced adenomas ²	1 (0–2)	0 (0–1)	<0.001

CI, confidence interval; SSA/P, sessile serrated adenoma/polyp; IQR, interquartile range.

¹ Proximal to sigmoid colon.

² Advanced adenomas: ≥ 10 mm in size, with villous component or high grade dysplasia.

Statistical analysis

Quantitative variables were summarized using mean (standard deviation [SD]) and median (interquartile range [IQR]) values for skewed data. Frequencies (%) were used to summarize categorical variables. Student's *t* test was used to compare continuous variables with a normal distribution and Mann–Whitney *U* test (unpaired) for those with skewed distribution. The chi-squared test was used to test associations among categorical variables. All statistical tests were two-sided, and *P* values <0.05 were considered statistically significant.

Multiple logistic regression was used to identify independent predictors of a diagnosis of SPS using backward stepwise variable selection. Candidate variables for inclusion in the model were those achieving a *P* value ≤0.1 in the univariable analysis. Odds ratios (ORs) and associated 95% confidence intervals (CIs) were used to quantify the level of association.

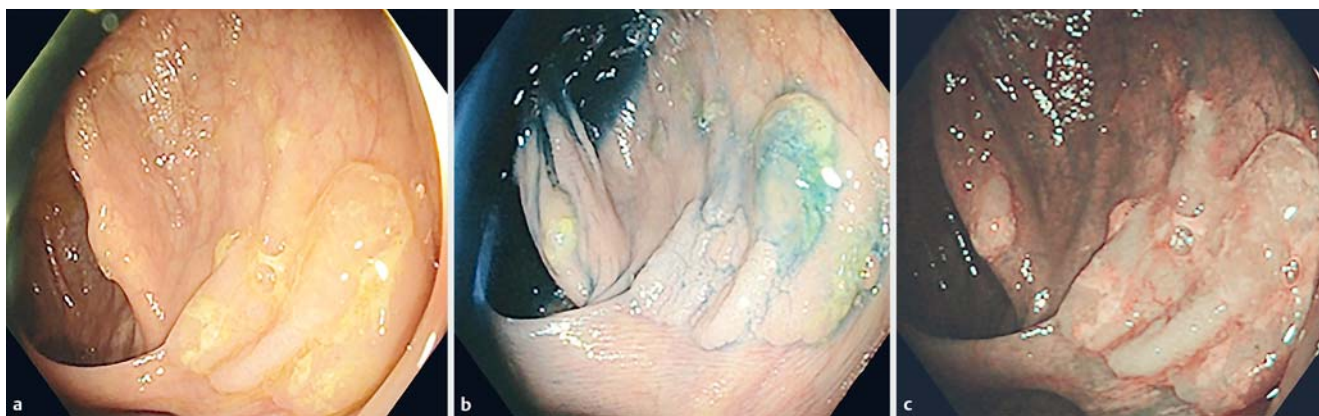
SPSS statistics software version 20.0 (SPSS Inc., Chicago, Illinois, USA) was used to analyze the data.

Results

Patients included in the study

From a total of 3444 patients who underwent a colonoscopy after a positive FIT, 201 individuals (5.8%) had one or more serrated lesions ≥5 mm proximal to the sigmoid colon (see ► **Fig. 2**). Five individuals who underwent colonoscopy in other centers (n=4) or with incomplete colonoscopy (n=1) were excluded.

Eleven patients (73% men; age 57 ± 3 years) fulfilled SPS criteria on their baseline colonoscopy. Among the remaining 185 patients, 114 followed the standard surveillance protocol based on adenoma burden, while 71 patients underwent a reassessment colonoscopy at 11.9 ± 1.7 months. As shown in ► **Table 1**, the demographic characteristics of both groups at baseline colonoscopy were comparable. As expected, patients who underwent a reassessment colonoscopy had a higher burden of polyps than patients scheduled for standard surveillance.



► **Fig. 3** Example of a large flat elevated (Paris classification 0-IIa) sessile serrated adenoma/polyp visualized with different endoscopic techniques: **a** high definition white-light endoscopy; **b** high definition conventional chromoendoscopy (with indigo carmine 0.4% dye); **c** electronic chromoendoscopy (narrow-band imaging [NBI]).

Rate of SPS diagnosis

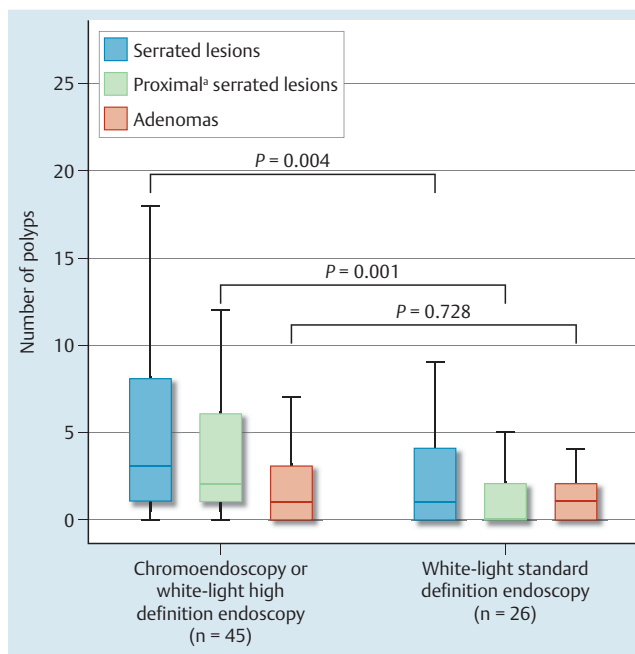
As mentioned above, 11/3444 patients (0.32%) were diagnosed with SPS on their baseline colonoscopy. As is shown in the ► **Fig. 2**, out of 71 patients who underwent reassessment colonoscopy, 20 new patients (45% men; age 58 ± 2 years) fulfilled SPS criteria (criterion 1 fulfilled [$n=9$], criterion 3 fulfilled [$n=6$], and criteria 1 and 3 both fulfilled [$n=5$]). Therefore, after reassessment colonoscopy, the rate of SPS increased to 0.90% (31/3444 patients). As expected, the patients diagnosed with SPS on their reassessment colonoscopy had significantly more serrated lesions than the 51 patients who were not diagnosed with SPS (median 15 [IQR 9–21] vs. 5 [2–9], respectively; $P < 0.001$). There were no significant differences in the numbers of adenomas.

Missed lesions detected on reassessment colonoscopy

The number of all missed lesions detected on reassessment colonoscopy was 5 [1–9], with missed lesions being more common in the proximal colon than in the distal colon to splenic flexure (5 [1–10] vs. 2 [1–7], respectively; $P < 0.001$). Serrated lesions were more often overlooked than adenomas (2 [0–6] vs. 1 [0–3], respectively; $P = 0.008$), with this difference also being evident when considering just the proximal colon (1 [0–4] vs. 0 [0–2], respectively; $P = 0.01$).

Usefulness of endoscopic techniques for reassessment colonoscopy

Among the reassessment colonoscopies, 41/71 (58%) were performed using chromoendoscopy, 37 of these being conventional (26 standard definition and 11 high definition) and 4 being electronic (► **Fig. 3**). The remaining 30 colonoscopies (42%) were performed using white light alone (26 standard definition and 4 high definition). The use of chromoendoscopy or high definition endoscopes at reassessment colonoscopy was not related to polyp burden at baseline colonoscopy (► **Table 2**).



► **Fig. 4** Usefulness of advanced endoscopic techniques for the detection of different lesions on reassessment colonoscopy. ^a Proximal to sigmoid colon.

The number of serrated lesions detected with chromoendoscopy was higher than with white light alone (3 [1–9] vs. 1 [0–5], respectively; $P = 0.046$) regardless of the type of endoscope used. The number of serrated lesions detected with high definition white light was higher than with standard definition white light (6 [4–8] vs. 1 [0–4], respectively; $P = 0.03$). When analyzing the colonoscopies performed with standard definition endoscopes, the number of serrated lesions detected with chromoendoscopy was higher than with white light alone (3 [1–9] vs. 1 [0–4], respectively; $P = 0.008$). Therefore, as is shown in ► **Fig. 4**, the use of chromoendoscopy and/or high definition endoscopes results in the detection of significantly

Table 2 Findings on baseline colonoscopy and effect of image-enhancement techniques and type of endoscope used at reassessment colonoscopy.

Finding on baseline colonoscopy	Reassessment colonoscopies (n = 71)	Image-enhancement techniques			Type of endoscope			P value	Odds ratio ³ (95%CI)	Standard definition ² (n = 52)	P value
		Chromo-endoscopy ¹ (n = 41)	White-light endoscopy ² (n = 30)	White-light endoscopy ² (n = 30)	High definition (n = 19)	Odds ratio ³ (95%CI)					
1 – 2 serrated lesions <10mm	13	46%	54%	54%	15%	0.56 (0.16 – 1.89)	0.35	0.43 (0.08 – 2.19)	84%	0.31	
≥ 1 serrated lesion with dysplasia	8	50%	50%	50%	13%	0.70 (0.16 – 3.06)	0.71	0.35 (0.04 – 3.11)	87%	0.67	
3 – 4 serrated lesions <10mm	9	67%	33%	33%	33%	1.54 (0.35 – 6.73)	0.73	1.43 (0.32 – 6.43)	67%	0.69	
1 – 2 serrated lesions ≥ 10mm	11	45%	55%	55%	18%	0.55 (0.15 – 2.02)	0.51	0.56 (0.11 – 2.87)	82%	0.72	
3 – 4 serrated lesions ≥ 10mm	34	59%	41%	41%	23%	1.08 (0.42 – 2.79)	0.86	0.72 (0.25 – 2.10)	77%	0.56	
≥ 5 proximal ⁴ serrated lesions	29	62%	38%	38%	34%	1.35 (0.51 – 3.54)	0.54	1.93 (0.66 – 5.58)	66%	0.22	
1 SSA/P	18	56%	44%	44%	28%	0.88 (0.30 – 2.60)	0.83	1.07 (0.32 – 3.55)	72%	0.91	
≥ 2 SSA/Ps	25	72%	28%	28%	72%	2.57 (0.90 – 7.32)	0.07	1.10 (0.36 – 3.28)	28%	0.86	
≥ 2 SSA/Ps ≥ 10 mm	11	73%	27%	27%	18%	2.18 (0.52 – 9.03)	0.34	0.56 (0.11 – 2.87)	82%	0.72	

CI, confidence interval; SSA/P, sessile serrated adenoma/polyp.

¹ Chromoendoscopy: conventional (i.e. indigo carmine 0.4% dye spraying) or electronic (i.e. narrow-band imaging).

² White-light endoscopy and use of a standard definition endoscope were the respective reference groups.

³ Univariable analysis.

⁴ Proximal to the sigmoid colon.

► Table 3 Univariable and multivariable analysis of factors predictive of a diagnosis of serrated polyposis syndrome (SPS) at reassessment colonoscopy.

Risk factors	Number of reassessment colonoscopies (n=71)	SPS (n=20)	Non-SPS ¹ (n=51)	Univariable analysis		Multivariable analysis	
				Odds ratio (95%CI)	P value	Adjusted odds ratio (95%CI)	P value
Sex, female	36	31%	69%	1.27 (0.45–3.58)	0.65	–	–
Age, 50–60 years old ²	43	30%	70%	0.76 (0.26–2.25)	0.63	–	–
1–2 serrated lesions <10 mm ³	13	0%	100%	–	0.01	–	–
≥1 serrated lesions with dysplasia ³	8	62%	38%	5.3 (1.13–24.98)	0.04	–	–
3–4 serrated lesions <10 mm ³	9	11%	89%	0.28 (0.03–2.42)	0.43	–	–
1–2 serrated lesions ≥10 mm ³	11	18%	82%	0.51 (0.10–2.643)	0.72	–	–
3–4 serrated lesions ≥10 mm ³	34	35%	65%	1.97 (0.690–5.66)	0.20	–	–
≥5 proximal ⁴ serrated lesions ³	29	45%	55%	4.06 (1.36–12.11)	0.01	4.01 (1.20–13.45)	0.02
1 SSA/P ³	18	33%	67%	1.39 (0.43–4.41)	0.57	–	–
≥2 SSA/Ps ³	25	48%	52%	4.38 (1.46–13.09)	0.006	–	–
≥2 SSA/Ps ≥10 mm ³	11	64%	36%	6.32 (1.61–24.98)	0.004	6.35 (1.40–28.81)	0.02
Chromoendoscopy ⁵ and/or high definition endoscopes at reassessment colonoscopy	41	37%	63%	2.88 (0.912–9.12)	0.07	4.99 (1.11–22.36)	0.04

CI, confidence interval; SSA/P, sessile serrated adenoma/polyp.

¹ Non-SPS group as the reference group.

² 60–69 years as reference group.

³ On baseline colonoscopy.

⁴ Proximal to the sigmoid colon.

⁵ Chromoendoscopy: conventional (indigo carmine 0.4% dye spraying) or electronic (narrow-band imaging).

more serrated lesions and proximal serrated lesions. The endoscopic technique did not affect the adenoma detection.

Factors predictive of SPS being diagnosed on reassessment colonoscopy

We evaluated factors on the baseline colonoscopy that were predictive of SPS being diagnosed in our cohort of individuals empirically scheduled for a reassessment colonoscopy (► **Table 3**).

Univariable analysis showed that the presence of five or more proximal serrated lesions (OR 4.06, 95%CI 1.36–12.11; $P=0.01$), two or more SSA/Ps (OR 4.38, 95%CI 1.46–13.09; $P=0.006$), and two or more SSA/Ps ≥10 mm (OR 6.32, 95%CI 1.61–24.98; $P=0.004$) were significantly associated with the diagnosis of SPS on reassessment colonoscopy. Conversely,

none of the SPS patients had just one or two serrated lesions <10 mm on baseline colonoscopy.

Multivariable analysis adjusted by age and sex showed that the presence of five or more proximal serrated lesions (OR 4.01, 95%CI 1.20–13.45; $P=0.02$) or two or more SSA/Ps ≥10 mm (OR 6.35, 95%CI 1.40–28.81; $P=0.02$) were independent predictors of SPS being diagnosed on reassessment colonoscopy.

The use of chromoendoscopy and/or high definition white-light endoscopes at reassessment colonoscopy was also an independent predictor of SPS being diagnosed (OR 4.99, 95%CI 1.11–22.36; $P=0.04$).

Discussion

This is the first study to assess a diagnostic strategy that substantially improves the detection of SPS in patients. For patients with proximal serrated lesions on their baseline colonoscopy, a reassessment colonoscopy within 1 year tripled the total number of SPS diagnoses made in a FIT-based CRC screening program. Indeed, the rate of diagnosis of SPS increased from 0.32% (11 patients) after the baseline colonoscopy to 0.90% (20 additional patients) after the reassessment colonoscopy.

Despite different methodology and endpoints, our results are consistent with a recent multicenter study from five European CRC screening programs (three FOBT-based cohorts, to which our center contributed with a part of the Spanish cohort, and two primary colonoscopy cohorts) [13]. This study reported a rate of SPS of 0%–0.5% on baseline colonoscopy, with an increase of 0.4%–0.8% after follow-up. Moreover, a recent systematic review from six screening populations showed a rate of SPS of 0%–0.66% on baseline colonoscopy, being higher in FOBT-based screening cohorts (0.34%–0.66%) and lower in primary colonoscopy cohorts (0%–0.09%) [15].

This increase in SPS prevalence [2, 3, 13, 15] is attributed to greater clinical and pathological awareness and better endoscopic diagnostic accuracy [16, 17]. The diagnosis of SPS depends directly on one's ability to detect serrated lesions, which are often easily overlooked because of their imperceptibility [4].

The considerable variability in the rates of serrated lesions in the average risk population (from 1% to 27%) [13, 18] and the FOBT-based preselected population (from 15% to 19%) [13] supports the idea that serrated lesions are more often missed than adenomas. Tandem colonoscopy studies have shown a substantial adenoma miss rate of 20%–24% [19, 20]. Thus far, no study has specifically addressed the miss rate for serrated lesions. Our study demonstrates that a reassessment colonoscopy performed within 1 year consistently detects higher numbers of serrated lesions than adenomas (2 [0–6] vs. 1 [0–3], respectively; $P=0.008$). Although we cannot rule out that some of these polyps could be newly grown polyps that have developed during the year, it is more likely that they were overlooked at the time of baseline colonoscopy. Therefore, the serrated lesion miss rate is likely to be much higher than that reported for adenomas.

The significance of serrated lesions has escalated in importance in recent years and 20%–30% of all CRCs are thought to develop through the serrated neoplasia pathway. It has been hypothesized that poor detection [18] and subtotal resection of serrated lesions [21] are responsible for the relative failure of colonoscopy to protect against CRC in the proximal colon [8], which leads to an increase risk of interval CRC. Two recent studies [22, 23], including the largest cohort of SPS patients so far reported, showed 5-year cumulative incidences for CRC during surveillance of 1.9% and 1.5%. This CRC risk associated with SPS is certainly much lower than previously reported. However, the prevalence of CRC at the moment of SPS diagnosis was 29.3% [22] and 15.8% [23]. These data support the importance of a proper diagnostic approach in these patients and of subsequent

surveillance with highly proficient colonoscopies being performed by specialist endoscopists.

The endoscopists' meticulousness and optical training in the detection of serrated lesions are key factors for SPS diagnosis: endoscopists with a high adenoma detection rate may find 7– to 18-fold more serrated lesions than are found by endoscopists with lower detection rates [18, 24]. In the present study, all colonoscopies were performed in the setting of an organized CRC screening program with high standards of quality by expert endoscopists who were aware of high risk conditions [2].

The reassessment colonoscopy was specifically directed to the detection of serrated lesions; therefore high definition endoscopes and image enhancement techniques, such as chromoendoscopy (conventional or electronic), were used in 63% of patients. To date, there are scarce data on the potential of advanced endoscopy to improve SPS diagnostic yields. The use of high definition white-light endoscopy has been associated with a higher prevalence of proximal serrated lesions in an average risk population [16]. Conventional chromoendoscopy has never been formally assessed in this very specific setting; however, it has been shown to increase polyp detection (especially hyperplastic polyps) in an average risk population [25] and in high risk conditions, such as Lynch syndrome [26] and long-standing ulcerative colitis [27]. The usefulness of NBI is still controversial: in SPS patients, although a single center tandem study showed that NBI was superior to high definition white light for detecting serrated lesions [28], a multicenter tandem study showed no significant differences in the serrated lesion miss rates for the two techniques [29].

In our series, the use of chromoendoscopy (either conventional or electronic) and high definition endoscopes at reassessment colonoscopy was associated with higher detection specifically of serrated lesions, but not of adenomas, and was an independent factor for the diagnosis of SPS on reassessment colonoscopy. Therefore, our results provide a rationale for recommending the use of chromoendoscopy and/or high definition endoscopes to increase the diagnostic yield in the detection of serrated lesions. More studies are needed to assess the true clinical impact of this strategy.

Traditionally, surveillance guidelines have focused on conventional adenomas and have not considered serrated lesions. In fact, only recent guidelines have included serrated lesions in their algorithms, recommending: annual colonoscopies for patients who fulfil at least one SPS criteria; surveillance colonoscopy at a 3-year interval for patients with at least one TSA, serrated lesion, or SSA/P ≥ 10 mm or with a dysplastic component; and surveillance colonoscopy at a 5-year interval for patients with at least one small (< 10 mm) SSA/P without dysplasia [6]. However, these recommendations are based on the consensus opinion of experts without solid evidence [8].

In our study, the presence of five or more proximal serrated lesions or two or more SSA/Ps ≥ 10 mm on baseline colonoscopy increased the chances of having SPS by four- and six-fold, respectively. Although these baseline factors may be biased by initial patient selection, we consider that they may be a useful threshold to recommend a 1-year surveillance colonoscopy. Certainly, prospective studies are required to validate these results.

The present study encompasses a large population and provides new and interesting insights that are reflective of a real clinical setting. However, several limitations should be acknowledged and, although data were prospectively collected and were not reinterpreted, the retrospective design of the study certainly limits the generalization of the results.

First, reassessment colonoscopy was indicated in an individualized and non-structured way, which could imply a selection bias. In fact, a fraction of patients who also had at least one large and/or proximal serrated lesion did not undergo reassessment colonoscopy. However, decisions were taken based on the burden of serrated lesions by a dedicated multidisciplinary team in the context of an organized population-based screening program. Moreover, none of the patients who underwent standard surveillance (28/114) has been diagnosed with SPS.

Second, the endoscopic techniques used during the study were heterogeneous. The higher proportion of high definition endoscopes and advanced ancillary techniques (chromoendoscopy) used during reassessment colonoscopy could have introduced a major advantage for the detection of serrated lesions, thereby artificially enhancing the increase in diagnostic accuracy. If all baseline colonoscopies had been performed with high definition white-light endoscopes and/or chromoendoscopy, more than 11 SPS patients would probably have been detected initially and, consequently, the yield of the reassessment colonoscopy might have been lower. However, standard definition white-light endoscopy is still the most widespread and routinely used technique in the West. To date, guidelines do not recommend high definition endoscopes or chromoendoscopy as standard use for screening. Moreover, in the present study, the choice of the technique was subject to instrumental availability and was not related to the baseline characteristics of the patient.

On the other hand, reassessment colonoscopies were performed by a subgroup of five endoscopists who were obviously more motivated to detect serrated lesions. This increased awareness could have influenced the higher detection of serrated lesions at reassessment colonoscopy. However, the similar adenoma detection rate of all of the endoscopists performing baseline colonoscopies indicates that, without the reassessment colonoscopy, most of these SPS patients would in any case have been missed.

Finally, the potential drawback of interobserver variability among pathologists for differentiation between microvesicular hyperplastic polyps and SSA/Ps was minimized by using as the main outcome a variable that compiled all of the serrated lesion subtypes (SSA/P, hyperplastic polyp, and TSA) together. Moreover, histological interpretation was performed following the updated WHO 2010 guidelines [8].

In summary, we have confirmed that SPS is an underdiagnosed condition, even in the setting of an organized FIT-based CRC screening program with high quality colonoscopies. A high index of suspicion and the proper training in detection of serrated lesions are the keys to detecting these high risk patients. A feasible diagnostic strategy of a 1-year reassessment colonoscopy in individuals with proximal serrated lesions has shown a high yield, having tripled the rate of patients with SPS. The

presence of five or more proximal serrated lesions or two or more SSA/Ps ≥ 10 mm on baseline colonoscopy could be considered thresholds to indicate the need for reassessment colonoscopy. This colonoscopy should preferably be performed with the help of chromoendoscopy and high definition endoscopes. Further prospective studies are required to validate these results and adjust surveillance recommendations in patients with serrated lesions.

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Competing interests

None

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