ORIGINAL ARTICLE

Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study

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ABSTRACT

Objective Serrated polyposis syndrome (SPS) is associated with an increased colorectal cancer (CRC) risk, although the magnitude of the risk remains uncertain. Whereas intensive endoscopic surveillance for CRC prevention is advised, predictors that identify patients who have high CRC risk remain unknown. We performed a multicentre nationwide study aimed at describing the CRC risk in patients with SPS and identifying clinicopathological predictors independently associated with CRC.

Design From March 2013 through September 2014, patients with SPS were retrospectively recruited at 18 Spanish centres. Data were collected from medical, endoscopy and histopathology reports. Multivariate logistic regression was performed to identify CRC risk factors.

Results In 296 patients with SPS with a median follow-up time of 45 months (IQR 26–79.7), a median of 26 (IQR 18.2–40.7) serrated polyps and 3 (IQR 1–6) adenomas per patient were detected. Forty-seven patients (15.8%) developed CRC at a mean age of 53.9±12.8, and 4 out of 47 (8.5%) tumours were detected during surveillance (cumulative CRC incidence 1.9%). Patients with >2 sessile serrated adenomas/polyps (SSA/Ps) proximal to splenic flexure and ≥1 proximal SSA/P with high-grade dysplasia were independent CRC risk factors (incremental OR=2, 95% CI 1.22 to 3.24, p=0.006). Patients with no risk factors showed a 55% decrease in CRC risk (OR=0.45, 95% CI 0.24 to 0.86, p=0.01).

Conclusions Patients with SPS have an increased risk of CRC, although lower than previously published. Close colonoscopy surveillance in experienced centres show a low risk of developing CRC (1.9% in 5 years). Specific polyp features (SSA/P histology, proximal location and presence of high-grade dysplasia) should be used to guide clinical management.

Significance of this study

What is already known on this subject?

- Serrated polyposis syndrome is a condition associated with an increased personal and familial colorectal cancer (CRC) risk, although the magnitude of the risk remains uncertain.
- Intensive endoscopic surveillance to prevent CRC development is advised by several expert groups and scientific societies with scarce evidence.
- Clinicopathological predictors of CRC that could help identifying high-risk patients remain poorly understood.

What are the new findings?

- CRC is diagnosed in 15.8% of all patients who have serrated polyposis syndrome.
- Endoscopic colonoscopy surveillance performed in specialised centres is effective, with a cumulative risk of CRC of 1.9% in 5 years.
- The number of proximal sessile serrated adenomas/polyps and the presence of high-grade dysplasia in a proximal sessile serrated adenoma/polyp are able to identify patients at high-risk of developing CRC.

How might it impact on clinical practice in the foreseeable future?

- In patients with serrated polyposis syndrome, surveillance colonoscopy in specialised centres should be advised due to the increased CRC risk.
- Annual surveillance could be excessive, and should be tailored according to the presence of CRC risk factors in order to offer the optimal treatment and surveillance protocol for these patients.

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INTRODUCTION

Colorectal cancer (CRC) is currently one of the most common malignancies in developed countries,

and ranks second in cancer mortality.[1] Preventive strategies aim at identifying the disease at the earliest stages in at-risk individuals in order to decrease incidence and mortality.[2–4] Whereas conventional adenoma is still considered the precursor lesion of the majority of CRCs, the so-called serrated pathway has been proposed as an alternate mechanism of colorectal carcinogenesis, involved in up to 30% of all CRCs.[5 6] Thus, serrated polyps and especially sessile serrated adenomas/polyps (SSA/Ps) are currently recognised as CRC precursors.[6–8]

Serrated polyposis syndrome (SPS) is a condition characterised by the development of multiple serrated polyps throughout the colon, and has been defined by the WHO as the presence of (I) at least five serrated polyps proximal to the sigmoid colon, of which two measure at least 10 mm in diameter and/or (II) any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with SPS and/or (III) more than 20 serrated polyps spread throughout the colon.[9] Although this classification was established arbitrarily, it has been very helpful for standardising clinical diagnosis and comparison between studies. The prevalence of SPS remains unknown, but it is likely to be low in primary colonoscopy or sigmoidoscopy screening programmes (<0.1%).[10–12] However, the prevalence in preselected screening populations based on a positive faecal immunochemical test has been reported to be considerably higher (0.34%–0.66%).[13 14] Increased awareness, detection and precise endoscopic and histopathological characterisation of serrated polyps have likely improved the diagnosis of SPS, suggesting that the prevalence is greater than that previously published.[15 16]

Patients with SPS and their relatives are at increased risk of CRC. However, the overall CRC risk in SPS remains unknown. Several small retrospective studies have reported lifetime CRC risks ranging 7%–70%, being higher estimates probably biased due to small and selected series.[17–29] In addition, retrospective studies have shown that CRC can develop under colonoscopy surveillance.[17 18 22] Therefore, the US Multi-Society Task Force on Colorectal Cancer and the European Society of Gastrointestinal Endoscopy currently advise annual endoscopic surveillance for all patients with SPS.[30 31] Despite all the evidence gathered about CRC risk in patients with SPS during the last decade, clinicopathological predictors of CRC development remain poorly understood. As a consequence, the current intensive surveillance recommended for patients with SPS is likely to be excessive, and could be optimised based on personalised CRC risk factors.

The aims of our study were to describe the CRC risk in a large cohort of patients with SPS and identify specific predictive factors for CRC development. For this purpose, we conducted a multicentre nationwide study in the setting of a high-risk CRC clinic network, including the largest cohort of patients with SPS described so far.

PATIENTS AND METHODS

Study population

From March 2013 to September 2014, 18 Spanish centres retrospectively recruited patients who fulfilled the SPS diagnostic criteria as defined by the WHO International Classification.[9] Clinical data was analysed from 1993 to 2014, although the majority of patients (245/296 (82.8%)) were diagnosed since 2010. The diagnosis of SPS was based on the endoscopic and histopathological reports from all polyps removed at both colonoscopies and/or surgery. Only histologically confirmed serrated polyps were counted for the diagnosis. For this study, only patients fulfilling WHO criteria I and/or III were analysed. Patients with hereditary CRC syndromes (ie, *APC*, *MUTYH* and mismatch repair genes germline mutations), as well as patients with IBD, were not considered for the study. Patient data was stored in a centralised database. The institutional review board of each participating centre approved the study, and informed consent was obtained for all patients.

Clinical and demographic characteristics

Demographic data concerning age, sex, cigarette smoking history, body mass index and personal history of malignancies were ascertained. Information on personal characteristics was obtained at the time of recruitment. Age at SPS diagnosis was defined by calculating the time when the patient fulfilled the SPS WHO criteria. Family history of any malignancies in first-degree and second-degree relatives from unrelated patients with SPS was also collected. Detailed information regarding colorectal invasive tumours (size; morphology; tumour, node, metastases stage and location) was examined by evaluating both endoscopic and pathological reports. CRC detected during specific SPS surveillance and after a previous negative colonoscopy was defined as incident.

Endoscopic and surgical records

In the setting of high-risk clinics, experienced endoscopists performed clearing and surveillance colonoscopies, which essentially consisted removal of all polyps ≥3–5 mm at clearing colonoscopy (which usually requires more than one procedure), and subsequent surveillance colonoscopies scheduled every 1–2 years. Criteria for referring patients to surgery (CRC development, unresectable polyp or severe polyposis) and type of surgery (total colectomy/proctocolectomy or segmental colectomy) were also documented. Endoscopic parameters included procedure indication (screening, surveillance or symptoms), quality of bowel preparation and findings (ie, CRC, adenomas, serrated polyps and no neoplastic lesions), standard/high definition technology and use of ancillary endoscopic techniques (ie, panchromoendoscopy with indigo carmine or virtual chromoendoscopy, which were applied according to the clinical practice of each centre). Polyp parameters included number, size and location. Polyp location was divided in three segments: proximal colon (caecum, ascending and transverse colon), descending colon (splenic flexure and descending colon) and distal colon (rectosigmoid). With this categorisation, we could define the proximal colon as proximal to sigmoid or proximal to splenic flexure.

Histopathological records

Tissue specimens were routinely processed and reviewed by the expert GI pathologist of each participating centre. No centralised pathological review was performed for the purpose of the study. Serrated polyps were classified as hyperplastic polyp (HP), SSA/P and traditional serrated adenoma (TSA) based on the current WHO classification criteria.[9] Unclassified serrated polyps were only used for number, size and location analyses. Cytological dysplasia among SSA/Ps and TSAs was routinely classified as low-grade and high-grade dysplasia at each participating centre according to the Vienna criteria.[32] Intramucosal carcinoma and carcinoma in situ were included within the high-grade dysplasia group. Cytological dysplasia among serrated polyps was analysed both as 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. Advanced adenoma was

defined as an adenoma ≥10 mm in diameter, or with villous structure or high-grade dysplasia.

Statistical analysis

Statistical analysis was performed using SPSS V.20.0 (IBM, Somers, New York, USA). Quantitative variables are expressed as medians and IQR, or means and SD; categorical variables are expressed as total number and frequencies (%). Quantitative variables were analysed using Student's test, and qualitative variables were analysed using χ^2 test. Cumulative incidence of CRC was calculated by Kaplan–Meier survival analysis. Univariate binary logistic regression was performed for selecting variables associated with the presence of CRC. For multivariate logistic regression analyses, only candidate variables with p values ≤0.05 on univariate analysis were used in the final multivariate model. We included OR with 95% CIs to quantify the magnitude of the association.

RESULTS

Clinical features of patients with SPS

A total of 296 individuals were diagnosed as SPS according to WHO criteria I and/or III, with a median follow-up time of 45 months (IQR 26–79.7). Initial colonoscopy was indicated in asymptomatic patients in 165 (55.7%) cases, and 231 (78%) patients were diagnosed of SPS during screening/surveillance colonoscopies. Detailed demographic and clinical characteristics of the whole cohort are presented in table 1. The mean age at diagnosis of SPS was 57.2±9.9 years, with a small predominance in men (56.1%). Prevalence of overweight/obesity and smoking history was 69.5% and 74.4%, respectively. Eighty-seven out 296 (29.4%) patients reported a family history of CRC in first-degree relatives, although in only seven (8%) the relative with CRC was diagnosed before the age of 50 years. Family history of SPS in first-degree relatives was reported in 13 (4.4%) unrelated cases.

Regarding the colonic phenotype, 79 (26.6%) patients displayed preferentially large right-sided polyps (≥5 proximal serrated polyps, two of which ≥10 mm, corresponding to patients fulfilling criterion I alone), 134 (45.2%) displayed polyps throughout the colorectum (ie, criterion III) and 83 (28.2%) patients fulfilled both criteria I and III. Accordingly, 162 (54.7%) of our population fulfilled criterion I. Our study included a total of 13 (4.4%) that also fulfilled criterion II. Of these, seven patients fulfilled criteria II and III, five patients fulfilled criteria I, II and III and one patient fulfilled criteria I and II. There were no differences in age and gender across the different phenotype patterns (data not shown).

Concerning the clinical approach, 217 (73.3%) patients could be successfully managed endoscopically, and 79 (26.6%) patients underwent surgery due to either severe polyposis (n=32, 40.5%) or CRC development (n=47, 59.5%). In patients with CRC, 16 (34%) underwent a total colectomy with ileorectal anastomosis, and 31 (66%) underwent a segmental colectomy (right hemicolectomy in 14 (29.6%), sigmoidectomy in 10 (21.7%) and lower anterior resection in 7 (14.7%)). Among patients with severe polyposis, 19 (59.4%) underwent a total colectomy with ileorectal anastomosis, whereas a segmental colectomy was done in 13 (40.6%) (right hemicolectomy in 11 and left hemicolectomy in two).

Patients underwent a total of 1008 colonoscopies, 319 (31.6%) of them were surveillance procedures ((median per patient 2 (IQR 1–3)). The median interval between surveillance endoscopies was 16 months (IQR 12.6–21.4) months.

Polyp features

A total of 11 270 polyps were registered, including 9833 (87.2%) serrated polyps and 1437 (12.8%) adenomas. Concerning serrated polyps, polyp location was reported in 9374 (95.3%) specimens; 2987 (32.1%) were located proximal to the splenic flexure, 1485 (15.9%) in the descending colon and 4902 (52.7%) in the rectosigmoid. Complete histological classification of serrated polyps was described in 8903 (90.5%) specimens. Main polyp features according to WHO classification of serrated polyps subtypes are presented in table 2. Serrated polyps ≥10 mm (n=1155) were preferentially located in the proximal colon (proximal to the splenic flexure 709 (66.4%), descending colon 174 (16.3%), rectosigmoid 272 (23.9%)). Cytological dysplasia was present in 484 (5.4%) of serrated polyps, 450 (5%) had low-grade dysplasia and 34

Table 1 Baseline characteristics of patients with SPS (n=296)

Demographic and clinical features	
Age at diagnosis SPS (years), mean±SD	57.2±9.9
Female, n (%)	130 (43.9%)
BMI*, mean±SD	27.5±4.6
Overweight/obesity (BMI ≥25), n (%)	146 (69.5%)
Smoking history, n (%)†	207 (74.5%)
First-degree relative with CRC, n (%)	87 (29.4%)
First-degree relative with SPS, n (%)	13 (4.4%)
WHO criteria‡, n (%)	
I	79 (26.7%)
III	134 (45.3%)
I+III	83 (28%)
Follow-up since SPS diagnosis (months), median (IQR)	45 (26–79.7)
Number of total colonoscopies, median (IQR)	3 (2–4)
Cumulative number of serrated polyps (per patient)	
Serrated polyps, median (IQR)	26 (18.2–40.7)
Location, median (IQR)	
Proximal to splenic flexure	7 (4–14)
Descending colon	3 (1–6)
Rectosigmoid	11 (5–23.5)
Size, median (IQR)	
Serrated polyps ≥10 mm	2 (0–4)
Histology, median (IQR)	
Serrated polyp subtypes	
Hyperplastic polyp	17.5 (6–30.2)
Sessile serrated adenoma/polyp	3 (0–9)
Traditional serrated adenoma	0 (0–0)
Serrated polyp with dysplasia§	
Any dysplasia	0 (0–1)
LGD	0 (0–1)
HGD	0 (0–1)
Adenoma features	
Patients with ≥1 adenoma, n (%)	238 (80.4%)
Patients with ≥1 advanced adenoma¶, n (%)	131 (44.2%)
Number of adenomas (per patient), median (IQR)	3 (1–6)
Number of advanced adenomas¶ (per patient), median (IQR)	0 (0–1)

*Referred to 210 patients with available information.
†Smoking history includes both active and former smokers (referred to 278 patients with available information).
‡WHO criteria: (I) patients who fulfil criterion I only; (III) patients who fulfil criterion III only; (I+III) patients who fulfil both I and III criteria.
§Regardless of the serrated polyp subtype.
¶Advanced adenoma: ≥10 mm in diameter or with villous structure or with high-grade dysplasia.
BMI, body mass index; CRC, colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia; SPS, serrated polyposis syndrome.

Table 2 Characteristic of serrated polyps according to histological subtype

	Hyperplastic polyps	Sessile serrated adenomas/polyps	Traditional serrated adenomas
Total number, n (%)	6458 (72.5%)	2398 (27%)	47 (0.5%)
Size ≥10 mm, n (%)	359 (5.4%)	647 (28.7%)	27 (57.4%)
Location, n (%)			
▶ Proximal to splenic flexure	1520 (23.5%)	1330 (55.4%)	26 (55%)
▶ Descending colon	902 (14%)	446 (18.6%)	10 (21.2%)
▶ Rectosigmoid	4036 (62.5%)	622 (25.9%)	11 (23.8%)
Cytological dysplasia, n (%)			
▶ Any dysplasia		469 (19.5%)	15 (31.5%)
▶ Low-grade dysplasia		438 (18.2%)	12 (25.5%)
▶ High-grade dysplasia		31 (1.4%)	3 (6.4%)

(0.4%) had high-grade dysplasia. Regarding adenomas, a total of 1437 adenomas were collected, of which, 270 (18.7%) were advanced adenomas (89 (6.2%) had high-grade dysplasia, 200 (13.9%) were ≥10 mm and 142 (9.8%) displayed villous histology).

Cumulative number of polyps per patient is presented in table 1. A median of 26 (IQR 18.2–40.7) serrated polyps per patient was found. Sessile serrated adenomas/polyps were found in 193 (65.2%) patients, 143 (48.3%) of them displayed SSA/Ps ≥10 mm and 84 (28.3%) displayed SSA/P with cytological dysplasia (73 (24.6%) patients showed low-grade dysplasia and 18 (6%) high-grade dysplasia). In our study, 239 (80.7%) patients had at least one adenoma, and 131 (44.2%) of them had advanced adenomas.

Table 3 Colorectal features of CRCs diagnosed in patients with SPS

N=47 (15%)	
Age at CRC diagnosis (years), mean±SD	53.9±12.8
WHO criteria*, n (%)	
▶ Criterion I	14 (29.7%)
▶ Criterion III	19 (40.6%)
▶ Criteria I+III	14 (29.7%)
Tumour location, n (%)	
▶ Caecum	3 (6.4%)
▶ Ascending colon	6 (12.8%)
▶ Hepatic flexure	3 (6.4%)
▶ Transverse colon	10 (21.3%)
▶ Descending colon	1 (2.1%)
▶ Sigmoid colon	18 (38.3%)
▶ Rectum	6 (12.8%)
TNM tumour stage, n (%)	
▶ I	24 (51%)
▶ II	12 (25.5%)
▶ III	6 (12.8%)
▶ IV	5 (10.7%)
Time at CRC diagnosis, n (%)	
▶ Before SPS diagnosis	8 (17%)
▶ At the time of SPS diagnosis	35 (74.5%)
▶ During SPS surveillance	4 (8.5%)

*WHO criteria: (I) patients who fulfil criterion I only; (III) patients who fulfil criterion III only; (I+III): patients who fulfil both I and III criteria.
CRC, colorectal cancer; SPS, serrated polyposis syndrome; TNM, tumour, node, metastases.

Prevalence of CRC in patients with SPS

Of the 296 patients included in the study, 47 (15.8%) developed CRC at a mean age of 53.9±12.8; 22 (46.8%) were female. Clinical and pathological features of these cases are summarised in table 3. CRC prevalence was similar across the different colonic phenotypes (criterion I vs III vs I+III), and tumours were equally distributed throughout the colon (22 (46.8%) cases were located in the proximal colon and 25 (53.2%) in the distal colon). The mean age at CRC diagnosis was younger for patients fulfilling criterion III (46.7 years) compared with patients fulfilling criterion I (56.9 years) or criteria I and III (55.1 years), although this difference was not statistically significant (p=0.2 and p=0.81, respectively). Tumours were preferentially diagnosed at early stages (76.5% were at stage I and II). While CRC was diagnosed at the time of initial colonoscopy in 35 (74.5%) patients, the diagnosis of CRC was made before the diagnosis of SPS in eight (17%) patients (median time between CRC and SPS diagnosis 10.7 years (IQR 5.5–28.1)).

Four (8.5%) individuals developed CRC during surveillance at mean age of 62.5±6.2 years (figure 1). The cumulative CRC risk for patients with SPS with no prior history of CRC (267/296, 90.2%) was 1.9% with a mean follow-up of 4.9 years

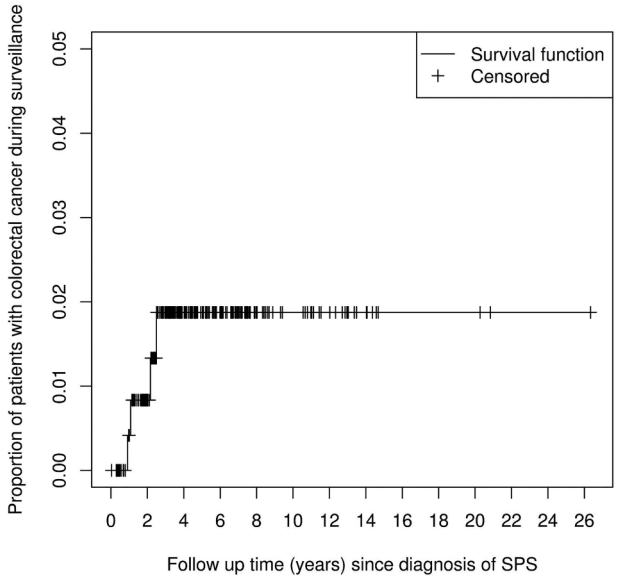

Figure 1 Proportion of patients with colorectal cancer during surveillance and follow-up time (years) since diagnosis of serrated polyposis syndrome (SPS).

(figure 1). The median time from the previous surveillance colonoscopy to CRC development in this group was 12 months (IQR 7.25–20.5), with a median of 2.5 (IQR 2–6) surveillance colonoscopies per patient. Main features of patients diagnosed with CRC during surveillance are detailed in table 4. In all four patients, CRC was detected during a scheduled endoscopy without any clinical symptoms, and all previous procedures were regarded as quality colonoscopies (defined as colonoscopies that reached the caecum and adequate bowel preparation). All tumours were diagnosed at an early stage except a rare case of a mixed adenoneuroendocrine carcinoma diagnosed in a 54-year-old woman.[33] In this case (patient 2), a non-granular lateral spreading tumour of 25 mm size was diagnosed at a surveillance colonoscopy performed 13 months after the previous colonoscopy, with biopsies revealing an adenocarcinoma. Patient underwent a total colectomy, and the surgical specimen showed an aggressive tumour, with marked lymphovascular invasion, mucinous features and 70% of neuroendocrine component. In another patient (patient 3), tumour was detected only 6 months after previous clearance colonoscopy. In this case, an 18 mm polyp (Paris 0-Is+IIa) was found in the ascending colon with histology of adenocarcinoma. Total colectomy was performed, and the surgical specimen exhibited an invasive adenocarcinoma within an SSA/P with high-grade dysplasia. In patient 4, CRC developed in a small polyp (4 mm) located in the sigmoid colon 11 months after the previous surveillance colonoscopy.

Variables associated with CRC in patients with SPS

Demographic, clinical and polyp features of patients with SPS with and without CRC are summarised in table 5. Univariate analysis demonstrated that no demographic or clinical features were associated with CRC. Regarding the polyp features, patients with CRC had significantly more SSA/Ps than patients without CRC (4 vs 2, p=0.024). In addition, when several polyp features were combined (see online supplementary table S1), we observed that the number of SSA/Ps with high-grade dysplasia (p=0.047), the number of SSA/Ps proximal to the sigmoid (4 vs 2, p=0.007) and proximal to the splenic flexure (3 vs 1, p=0.005), and the number of SSA/Ps with high-grade dysplasia proximal to the splenic flexure (p=0.016) were the most significant variables associated with CRC development. Neither the number of adenomas nor advanced adenomas was associated with CRC.

We next performed a multivariate logistic regression including those variables found to be significantly associated with CRC in patients with SPS (table 6), adjusting for age and gender. The number of SSA/Ps proximal to the splenic flexure (OR=1.04, 95% CI 1.01 to 1.07, p=0.016) and the number of SSA/Ps proximal to the splenic flexure with high-grade dysplasia (OR=2.12, 95% CI 1.04 to 4.5, p=0.049) were independently associated with CRC in patients with SPS. In order to provide an easier and more useful clinical application of these findings, we categorised the independent variables associated with CRC into binary variables. Hence, after statistical evaluation of the most meaningful cut-offs, we found that patients with more than two proximal SSA/Ps (present in 26/47 (55.3%) patients with CRC and 92/249 (36.9%) patients without CRC; OR=2.11, 95% CI 1.012 to 3.96, p=0.02) and those with any proximal SSA/P with high-grade dysplasia (present in 6/47 (12.7%) patients with CRC and 12/249 (4.8%) patient without CRC; OR=2.90, 95% CI 1.03 to 8.13, p=0.03) were at a significantly increased risk compared with patients with none of these criteria.

When we combined the two independent CRC predictors found in this study (ie, >2 proximal SSA/Ps and ≥1 SSA/P with high-grade dysplasia), we were able to outline three risk categories: (I) patients with no risk factors, (II) patients with either of the two risk factors and (III) patients with both risk factors (table 7). When compared with patients with SPS with no risk factors, we observed a twofold linear increasing probability of developing a CRC for each additional risk factor (incremental OR=2, 95% CI 1.23 to 3.3, p=0.006). Moreover, patients with SPS with no risk factors showed a 55% CRC risk reduction (OR=0.45, 95% CI 0.24 to 0.86, p=0.01).

DISCUSSION

This multicentre cohort study represents the largest published series of patients with SPS strictly selected according to the most recent WHO criteria, and shows that CRC is diagnosed in 15.8% of patients, the great majority of them simultaneously to the diagnosis of SPS. Our results also demonstrate that CRC risk is independently associated with specific phenotypic characteristics of serrated polyps. Indeed, the number of proximal SSA/Ps and the presence of high-grade dysplasia in proximal SSA/Ps are able to identify patients at high risk of developing CRC. Moreover, close surveillance with annual colonoscopy in patients with SPS is effective for CRC prevention in the majority of patients, with a cumulative risk of CRC of 1.9% in 5 years. Overall, our results indicate that intensive surveillance should be tailored according to the presence of risk factors in order to offer the optimal treatment and surveillance protocol for patients with SPS.

Consistent with previous series of patients with SPS, our results corroborate that this syndrome occurs both in males and females aged between 50 and 60 years.[17 22] Cigarette smoking history and overweight/obesity, conditions previously associated with an increased risk of developing serrated polyps,[34–38] were widespread in our patients (nearly 70% and 75% of patients, respectively), suggesting a potential causative or predisposing role. Since most patients with SPS develop the colonic polyposis over the age of 50 years with no family history of colorectal neoplasia, the association with environmental factors suggests that for most cases, SPS is not an inherited genetic syndrome and rather behaves as a complex disorder where disease appears as a consequence of the interaction of genetic susceptibility and environment. Nevertheless, several lines of evidence suggest that a proportion of SPS could be the phenotypic expression of an inherited genetic syndrome. First, a significant proportion of patients with SPS report family history of CRC, and a few show first-degree relatives with SPS.[18 22 25 27 39] Second, first-degree relatives of patients with SPS appear to have an increased risk for both CRC and SPS,[40–43] and finally, patients with SPS display an unrelenting and rapid development of colorectal neoplasia.[17 18 28 44] We documented that 30% of patients with SPS have a first-degree relative with CRC and 4.5% show a first-degree relative with SPS, figures slightly lower than previously reported.[18 22 25 39 40] These observations suggest that for a minority of cases, a genetic basis is yet to be discovered. Until that moment, it is prudent to recommend screening colonoscopies in first-degree relatives as previously suggested.[43]

Although it is well established that SPS is associated with an increased risk of CRC, the exact lifetime risk and its clinical features remain uncertain. Initial small series of patients with SPS reported up to 70% rates of CRC[20 24–27] a figure that probably traduced an important selection bias overestimating the perception of CRC in SPS. The prevalence of CRC in subsequent studies, with a larger number of patients, described a lower risk

Table 4 Characteristics of patients with SPS with CRC diagnosed during surveillance

	Patient 1	Patient 2	Patient 3	Patient 4
Patient characteristics				
Age at SPS diagnosis, years	64	53	64	60
Age at CRC diagnosis, years	68	54	66	62
Gender	Male	Female	Male	Female
Endoscopic characteristics				
WHO criteria for SPS diagnosis	III	I+III	I+III	I+III
Number of serrated polyps/proximal* serrated polyps ≥10 mm	26/0	42/2	60/20	36/2
Number of SSA/P/proximal* SSA/P	1/1	33/28	58/58	32/31
Serrated polyps with high-grade dysplasia	No	No	Yes	Yes
Number of adenomas/advanced adenomas†	11/0	5/3	0/0	6/0
Number of surveillance colonoscopies (before CRC diagnosis)	3	2	2	7
Interval between previous surveillance colonoscopy and CRC diagnosis (months)	26	13	6	11
Indication for diagnostic colonoscopy	Surveillance	Surveillance	Surveillance	Surveillance
Tumour features				
Histology	Adenocarcinoma	MANEC	SSA/P+adenocarcinoma	Adenocarcinoma
Mucinous component	No	Yes	Yes	No
Lesion size (mm)	10	25	18	4
Location	Transverse colon	Transverse colon	Ascending colon	Sigmoid colon
Morphology‡	Ulcerated lesion	0-IIa+IIc	0-Is+IIa	0-IIa
Tumour staging (TNM)	I	IV	I	I

*Referred to the splenic flexure.
†Advanced adenoma: ≥10 mm in diameter or with villous structure or with high-grade dysplasia.
‡Based on the Paris classification.
CRC, colorectal cancer; MANEC, mixed adenoneuroendocrine carcinoma; SPS, serrated polyposis syndrome; SSA/P, sessile serrated adenoma/polyp; TNM, tumour, node, metastases.

between 7% and 35%.[17 22 23 39] Boparai *et al*,[17] in a retrospective multicentre study on 77 individuals with SPS, described a cumulative risk of CRC under colonoscopy surveillance of 6.5% in 5 years. In our cohort, we report that 15.8% of SPS develop CRC, the vast majority at the time of the initial colonoscopy, and only four patients developed CRC under endoscopic surveillance (cumulative CRC risk of 1.9% in 5 years). Interestingly, CRC occurs throughout the colon, with more than 50% of tumours located in the rectosigmoid. These observations suggest that although SPS is associated with an increased CRC risk, this risk is considerably lower than initially described. On the other hand, our results indicate that CRC incidence under colonoscopy surveillance performed by experienced endoscopists who are familiar with the management of this syndrome is fairly low and usually diagnosed at early stages. In agreement with this hypothesis, a recent prospective study performed in the Netherlands between 2007 and 2012, evaluating a standardised endoscopic treatment protocol in a large cohort of patients with SPS, showed that annual surveillance with complete removal of all polyps ≥3 mm prevented development of CRC in patients with SPS.[44] In our cohort, in three out of four patients with incident CRC during surveillance (patients 2–4), CRC could have arisen from serrated lesions that were either present at prior surveillance endoscopy, but were not removed, or were simply missed. Accordingly, high proficiency colonoscopy performed by specialised endoscopists is recommended. Although advanced imaging techniques (chromoendoscopy and narrow band imaging (NBI)) seem also advisable, current evidence is scarce. A recent study showed that NBI does not reduce polyp miss rates in patients with SPS compared with high-resolution white light endoscopy,[45] and chromoendoscopy has not been evaluated in this setting. Further studies are needed to elucidate the role of advanced endoscopy techniques in patients with SPS.

Despite all the evidence gathered regarding CRC risk in patients with SPS during the last decade, clinicopathological predictors of CRC development remain poorly understood. A previous retrospective study identified that the number of HPs (OR=1.05, 95% CI 1.01 to 1.1) and the number of serrated adenomas (which included both SSA/Ps and TSAs; OR=1.09, 95% CI 1 to 1.19) were independently associated with CRC.[17] However, analysis of other specific known factors associated with an increased risk of malignancy in serrated polyps such as proximal location, SSA/P histology or the presence of dysplasia[31 46 47] have not been accomplished. In our study, we performed a thorough evaluation of clinical, endoscopic and histopathological parameters that could identify patients with SPS at a higher CRC risk. The study design included the division of the colon in three segments (proximal colon referred to both splenic flexure and sigmoid colon, and rectosigmoid), thus allowing us to analyse the impact of polyp location in the CRC risk. Although adenomas and advanced adenomas were frequent in patients with SPS, conversely to previous reports, they were not associated with CRC.[48] However, patients with CRC had significantly more serrated polyps with SSA/P histology than patients without CRC. Multivariate logistic regression showed that increasing number of SSA/Ps proximal to the splenic flexure, especially the number of SSA/Ps proximal to the splenic flexure with high-grade dysplasia, was independently associated with CRC in patients with SPS. Polyp location proximal to the splenic flexure consistently showed a most robust association with CRC compared with the sigmoid colon. When we analysed the impact of the combination of these risk factors, we were able to define different risk groups in which the presence of each factor almost doubled the CRC risk. We believe that these results are of critical importance: on one hand, they support the hypothesis of a serrated pathway of carcinogenesis in at least a proportion of patients with SPS, and on the other hand, they

Table 5 Clinicopathological features associated with CRC in patients with SPS (univariate analysis)

Variable	CRC N=47 (15.8%)	No CRC N=249 (84.2%)	p value
Demographic and clinical features			
Age at SPS diagnosis: years, mean±SD	56.8±8.8	56.9±10.2	0.342
Female, n (%)	22 (46.8)	108 (43.4)	0.664
BMI*, mean±SD	27.1±5.1	27.7±4.5	0.425
Overweight/obesity (BMI ≥25), n (%)	22/39 (56.4)	124/171 (72.5)	0.051
Smoking history†, n (%)	30/45 (66.7)	177/233 (76)	0.193
First-degree relative with CRC, n (%)	9 (19)	78 (31)	0.097
First-degree relative with SPS, n (%)	1 (2)	12(4)	0.376
SPS WHO criteria‡, n (%)			
▶ Patients who fulfil criterion I	28 (59.6)	134 (46.2)	0.468
▶ Patients who fulfil criterion III	33 (70.2)	185 (74.3)	0.560
▶ Patients who fulfil criteria I and III	14 (29.8)	70 (28.1)	0.815
Follow-up time (months), median (IQR)	48 (24–79)	44 (26–80)	0.843
Number of colonoscopies, median (IQR)	3 (2–4)	3 (2–4)	0.315
Cumulative number of polyps (per patient), median (IQR)			
Serrated polyps			
Serrated polyps	26 (13–42)	26 (19–40)	0.326
Location			
▶ Proximal to splenic flexure	9 (4–16)	7 (4–13)	0.107
▶ Proximal to sigmoid colon	12 (5–28)	11 (6–19)	0.169
▶ Rectosigmoid	7 (4–21)	12 (5–24)	0.396
Size ≥10 mm	3 (0–6)	2 (0–4)	0.054
Specific subtype of serrated polyp			
▶ Sessile serrated adenoma/polyp	4 (1–14)	2 (0–8)	**0.040**
▶ Hyperplastic polyp	8 (0–24)	19 (8–33)	0.277
▶ Traditional serrated adenoma	0 (0–0)	0 (0–0)	0.516
Serrated polyps with dysplasia			
▶ Any dysplasia	0 (0–1)	0 (0–1)	0.496
▶ Low-grade dysplasia	0 (0–1)	0 (0–1)	0.961
▶ High-grade dysplasia	0 (0–0)	0 (0–0)	0.075
Combined features§			
▶ SSA/Ps proximal to splenic flexure	3 (0–11)	1 (0–4)	**0.005**
▶ SSA/P with high-grade dysplasia	0 (0–0)	0 (0–0)	**0.041**
▶ Proximal (to splenic flexure) SSA/P with high-grade dysplasia	0 (0–0)	0 (0–0)	**0.016**
Adenomas			
Number of adenomas	3 (1–6)	3 (1–6)	0.906
Number of advanced adenomas¶	1 (0–1)	0 (0–1)	0.910

Statistically significant results are represented in bold.
*Data concerning BMI were available for 207 patients.
†Smoking history includes both active and former smokers. Data concerning smoking history were available for 210 patients.
‡SPS WHO criteria: (I) patients who fulfil criterion I (regardless of criteria II and III); (III) patients who fulfil criterion III (regardless of criteria I and II); (I+III) patients who fulfil both criteria I and III (regardless of criterion II).
§Other variables related to SP combination features are widely reported in online supplementary table S1.
¶Adenomas ≥10 mm in diameter or with villous structure or with high-grade dysplasia.
BMI, body mass index; CRC, colorectal cancer; SP, serrated polyp; SPS, serrated polyposis syndrome; SSA/P, sessile serrated adenoma/polyp.

could have a clinical implication in defining high versus low risk groups. In our study, patients with SPS without any of the mentioned risk factors showed a 55% decrease in the CRC risk. Additional studies are needed to evaluate whether endoscopic surveillance can be performed at longer time intervals (ie, 1–3 years) in such low-risk patients.

Compared with previous studies, we believe our work has several strengths. First, our series represents the largest cohort of patients with SPS according to the current WHO criteria reported so far. Second, detailed endoscopic and pathological information was collected from a research network of experienced centres in the management of patients with SPS, and finally, this was a multicentre study in which the majority of patients were identified in a screening setting. Nevertheless, several potential limitations should also be acknowledged. First, as a retrospective study, selection bias could have influenced the results. Since patients were not systematically identified based on serrated polyps counts, a potential selection bias towards a more severe phenotype could exist. However, a subgroup analysis assessing CRC risk only in patients who were diagnosed through screening revealed a similar figure (22/165, 13.3%). Also, our study included eight cases in which the diagnosis of CRC was made before the diagnosis of SPS. Although colonoscopy data were not available for three out of eight patients, we assumed that those patients actually had SPS that was missed or unrecognised at that moment. Furthermore, due to the fact that no centralised review of the pathological specimens was performed, histological interpretation of serrated polyps could be

Table 6 Multivariate logistic regression of variables associated with colorectal cancer in patients with SPS

Variable	Adjusted OR	95% CI	Adjusted p value
Age at SPS diagnosis	1.02	0.98 to 1.05	0.256
Gender (female)	0.83	0.42 to 1.61	0.586
Number of SSA/Ps	0.97	0. 91 to 1.02	0.267
Number of SSA/Ps with HGD	0.76	0.29 to 2.92	0.678
Number of SSA/Ps proximal to the splenic flexure (per polyp)	**1.04**	**1.01 to 1.07**	**0.016**
Number of proximal (to splenic flexure) SSA/Ps with HGD (per polyp)	**2.12**	**1.01 to 4.50**	**0.049**

Statistically significant results are represented in bold.
HGD, high-grade dysplasia; SPS, serrated polyposis syndrome; SSA/P, sessile serrated adenoma/polyp.

heterogeneous between centres. Several reports have observed that SSA/Ps are usually misclassified as HPs, which may lead to an underestimation of SSA/P.[15] Even though most patients with SPS included in this study were diagnosed since 2005, when the current classification of serrated polyps was proposed,[8] this potential bias cannot be ruled out.[49] Second, although the WHO classification for serrated polyps does not recognise the distinction between low-grade and high-grade dysplasia in SSA/P,[9] our results suggest that high-grade dysplasia, as opposed to low-grade dysplasia, is associated with CRC development in patients with SPS. Indeed, multivariate analysis excluding subclassification of cytological dysplasia revealed the number of proximal SSA/P as the only CRC predictor (see online supplementary table S2). Future prospective studies with a central pathology review of the degree of cytological dysplasia by a group of expert pathologists are warranted to validate our results. Third, although in our study we observed a low incidence of CRC during surveillance (1.9% in 5 years), analysis of longer intervals are needed. Finally, although we found a strong and statistically significant association between certain endoscopic and histopathology variables and CRC risk, this association should not be regarded as causal. On one hand, since our study only had four incident CRCs, it was not powered enough to develop predictors of CRC development. On the other hand, previous evidence suggests that both serrated and conventional pathways of carcinogenesis coexist in patients with SPS.[5 6] In our study, despite the association of proximal SSA/P and CRC, in 50% of patients, tumours occurred in the rectosigmoid. Accordingly, further prospective studies are needed to clarify the relationship between histopathology factors identified in this study and CRC development.

Table 7 CRC risk groups in patients with SPS according to independent CRC risk factors

Variable	OR	95% CI	p value
No proximal SSA/P with HGD and ≤2 proximal SSA/Ps	1*	–	–
Any proximal SSA/P with HGD or >2 proximal SSA/Ps	1.98	1.02 to 3.81	0.04†
Any proximal SSA/P with HGD and >2 proximal SSA/Ps	4.27	1.30 to 14.03	0.01†
No proximal SSA/P with HGD and ≤2 proximal SSA/Ps	0.45	0.24 to 0.86	0.01‡

Proximal location refers to the splenic flexure.
*Reference category.
†Compared with the reference category.
‡Compared with patients fulfilling either of the two risk factors.
CRC, colorectal cancer; HGD, high-grade dysplasia; SPS, serrated polyposis syndrome; SSA/P, sessile serrated adenoma/polyp.

In conclusion, SPS is associated with an increased CRC risk (15.8%), although the magnitude of this risk is lower than previously published. Patients undergoing annual colonoscopy surveillance in experienced centres show a low risk of developing CRC (1.9% in 5 years). Specific polyp features (SSA/P histology, proximal location and presence of high-grade dysplasia) could be used to stratify the CRC risk of patients with SPS and offer longer surveillance intervals (1–3 years) in low-risk patients. Future studies should focus on patients with SPS undergoing a standardised treatment protocols in order to determine the best treatment and surveillance protocol for these patients.

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Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study

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