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Low Incidence of Advanced Neoplasia in Serrated Polyposis Syndrome After (Sub)total Colectomy: Results of a 5-Year International Prospective Cohort Study

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INTRODUCTION: Serrated polyposis syndrome (SPS) is accompanied by a substantially increased colorectal cancer (CRC) risk. To prevent or treat CRC in patients with a very high polyp burden, (sub)total colectomy with ileorectal or ileosigmoidal anastomosis is regularly performed. The CRC risk after (sub)total colectomy might be decreased, but evidence is lacking. We aimed to assess the yield of endoscopic surveillance in patients with SPS who underwent (sub)total colectomy.

METHODS: For this post hoc analysis, we used prospectively collected data from a large international prospective cohort study. We included patients diagnosed with SPS (World Health Organization type I and/or III) who underwent (sub)total colectomy. Primary endpoint was the cumulative 5-year incidence of CRC and advanced neoplasia (AN).

RESULTS: Forty-eight patients (mean age 61 ± 7.8; 52% men) were included and followed up for a median of 4.7 years (interquartile range 4.7–5.1). None of the patients developed CRC during follow-up. Five patients developed AN, corresponding to a cumulative 5-year AN incidence of 13% (95% confidence interval 1.2–23). In 4 patients, AN was diagnosed at the first surveillance endoscopy after study inclusion, and in 1 patient, AN was detected during subsequent rounds of surveillance. The risk of AN was similar for patients with ileorectal and ileosigmoidal anastomosis (logrank P = 0.83).

DISCUSSION: (Sub)total colectomy mitigates much of the excess risk of CRC in patients with SPS. Advanced neoplasms are mainly detected at the first endoscopy after (sub)total colectomy. Based on these results, after the first surveillance, intervals might be extended beyond the currently recommended 1–2 years.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B251 and http://links.lww.com/AJG/B252


INTRODUCTION

Serrated polyposis syndrome (SPS) is characterized by the presence of a high number of serrated polyps (SPs) in the colon. With a prevalence of up to 1:111 in fecal occult blood test (FOBT)-based screening populations, it is by far the most common colonic polyposis syndrome (1,2). SPS is associated with a substantial risk of colorectal cancer (CRC) (3–7). Because no genetic cause of SPS has been identified yet, its diagnosis is based on clinical criteria, defined by the World Health Organization (WHO) (8). These criteria currently include (i) at least

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5 SPs proximal to the sigmoid, with 2 or more of these being ≥10 mm; (ii) any number of SPs proximal to the sigmoid colon in an individual who has a first-degree relative with SPS; or (iii) >20 SPs of any size, distributed throughout the colon.

Up to 35% of patients with SPS have a personal history of CRC (3,4). Because most CRCs in patients with SPS occur before or at the time of SPS diagnosis, CRC is almost always the result of undiagnosed and/or untreated or insufficiently treated SPs (3,4). By contrast, if patients with SPS are adequately treated and systematically surveilled with colonoscopies, the incidence of CRC seems to be low according to the most recently published cohort studies (3,4,9).

To prevent CRC, the colon of patients with SPS should be cleared from premalignant polyps. Once cleared of such polyps, endoscopic surveillance is indicated (5,9–11). In most patients, clearance can be achieved endoscopically, without prophylactic surgery. However, a combination of excessive polyp burden, CRC, or unresectable polyps can demand surgical resection of the affected bowel segments.

In 2 recent cohort studies, 24%–27% of patients with SPS had undergone surgical intervention during the clearing phase, mostly because of CRC (59%–60%) and a high polyp burden (31%–41%). In 1 cohort, 35 of the 79 patients who required surgery underwent a total colectomy with ileorectal anastomosis, which was most often performed because of severe polyposis (3).

Thus, (sub)total colectomies are commonly performed in the management of SPS. However, the optimal endoscopic surveillance regimen after such extensive surgery is unknown. Although patients with only a short length of the rectosigmoid left in situ might not be at increased risk of developing CRC anymore, international surveillance guidelines recommend the same stringent surveillance intervals for patients with or without a history of (sub)total colectomy (10,12–15). We hypothesize that patients with SPS with a short length of the rectosigmoid left in situ are at low risk of developing CRC or advanced polyps during endoscopic surveillance. In a prospective international cohort study, we evaluated the yield of endoscopic surveillance in patients with SPS after (sub)total colectomy. In addition, we assessed whether the location of the anastomosis (ileorectal or ileosigmoidal) was related to the risk of subsequent advanced neoplasia (AN).

**METHODS**

**Study population and design**

This was a post hoc analysis of a prospective cohort study that was registered on the Dutch Trial Register (www.trialregister.nl; trial-ID 4609). All patients aged 18 years or older, fulfilling WHO SPS criteria I and/or III (8), were eligible for inclusion. Patients with SPS were recruited between January 2013 and April 2018. For the current study, only patients with a history of (sub)total colectomy with ileorectal or ileosigmoidal anastomosis who underwent post-operative surveillance were included in the analyses. Patients with SPS who were diagnosed before the start of this study could also be included. For these patients, only the surveillance data prospectively obtained within the timeframe of this study were taken into account for analysis. Patients with CRC-related germline mutations or inflammatory bowel disease were excluded.

The institutional review board of the Academic Medical Center decided that this study did not fall under the legislation
Histopathologic evaluation

All polyps were routinely reviewed by dedicated gastrointestinal pathologists. SPs were classified as hyperplastic polyp (HP), sessile serrated lesion (SSL) with or without dysplasia, or traditional serrated adenoma (TSA). All SPs with dysplasia or with a diameter of ≥10 mm and all TSAs were regarded as advanced SPs. Adenomas were diagnosed as tubular adenoma, tubulovillous adenoma (TVA, 25%–75% villous histology), or villous adenoma (≥75% villous histology). All adenomas ≥10 mm, with high-grade dysplasia or with ≥25% villous histology, were classified as advanced adenomas.

AN was defined as any advanced SPs, advanced adenomas, or CRCs.

Surveillance protocol

Before endoscopic surveillance, the colon of each patient had to be cleared from all polyps ≥5 mm and polyps ≥4 mm with the optical aspect of an adenoma, SSL, or TSA (thus, HPs 1–4 mm could be left in situ). Subsequent endoscopic surveillance was scheduled with intervals of either 1 or 2 years, based on polyp burden during the last endoscopy. Thus, the surveillance interval was redetermined after each consecutive surveillance endoscopy. An interval of 1 year was appointed to patients with one or more advanced polyps, or cumulatively ≥5 SSLs (irrespective of size), adenomas (irrespective of size), or HPs ≥5 mm, or if surgery was needed during the previous surveillance/clearing phase. In all other cases, a 2-year surveillance interval was recommended (see Figure, Supplementary Digital Content 1, http://links.lww.com/AJG/B251).

In case of violation of this protocol, patients were censored at the date the surveillance colonoscopy should have taken place, and only data before the protocol violation were used for our analyses. Violation of the protocol was defined as deviation from the required surveillance interval of ≥365 days.

Endoscopy quality

Routinely, standard and high-definition white-light endoscopes were used, and endoscopies were routinely performed at dedicated endoscopy programs. Based on the endoscopist’s preference, advanced...
endoscopic techniques such as (virtual) chromoendoscopy could be used. Bowel preparation was performed according to local practice and was judged using the Boston Bowel Preparation Scale. A Boston Bowel Preparation Scale of $2$ in all bowel segments was considered adequate, and in case of inadequate bowel preparation, a new endoscopy was scheduled, preferably within 6 months.

Outcome measures and statistical analyses
The primary outcome was the cumulative 5-year incidence of AN during postoperative surveillance, calculated with Kaplan-Meier analyses for all patients and stratified by the type of anastomosis (ileosigmoidal or ileorectal). Differences in AN incidence between anastomosis types were assessed with a logrank test. The location of anastomosis (ileosigmoidal or ileorectal) was extracted from surgical reports or, if surgical reports were not available, from endoscopy reports. Secondary outcome was the yield of nonadvanced and advanced polyps for each round of endoscopic surveillance. Statistical analyses were performed using RStudio version 1.1.453 (Integrated Development for R. RStudio, Boston, MA) with Survminer package version 0.4.3.

RESULTS
Between January 2013 and April 2018, 63 patients with a history of (sub)total colectomy were assessed for eligibility (Figure 1). Fourteen patients were excluded. Of which, nine were because they enrolled too late, and thus, their first surveillance was not yet due at study closure, 3 because they underwent proctocolectomy with ileoanal pouch reconstruction, and 2 because the study protocol was systematically not followed (2). Forty-eight patients with SPS were included in our analyses. They were followed up for a median of 4.7 years (interquartile range [IQR] 2.4–5.1 years; Table 1). Protocol violation led to early drop out of 3 patients (Figure 1).

Baseline characteristics
The mean age at inclusion was 61 years ($\pm 7.8$ years), and 52% were men. Most patients fulfilled both WHO criteria I and III (65%). Twenty-two patients had a history of CRC (46%), of whom 5 had multiple CRCs (3 synchronous and 2 metachronous). Of the 27 detected CRCs, 26 occurred before or during the clearing phase (96%), whereas 1 CRC (3.7%) was diagnosed after the clearing phase, but before study inclusion. Sixteen of the 27 tumors (59%) were located proximal to the splenic flexure. All but one CRC were diagnosed before or at the time of (sub)total colectomy. One patient was diagnosed with CRC after (sub)total colectomy, but before inclusion. However, in hindsight, it appeared that this patient had rather undergone an extended hemicolectomy instead of (sub)total colectomy with ileosigmoidal anastomosis because the endoscopist located this tumor in the transverse colon at 45 cm from the anal verge.

Protocolized surveillance endoscopies
A total of 104 surveillance endoscopies were performed, with a median of 2 per patient (IQR 1–3). Forty-six percent of patients were diagnosed with SPS before our study started and had thus undergone one or more surveillance endoscopies before study inclusion. Fifty-four percent were diagnosed with SPS during or shortly before our study and, thus, underwent their first surveillance endoscopy during the study. All patients underwent at least 1 round of protocolized surveillance, followed by a second, third, and fourth round in 34, 14, and 2 patients, respectively (Figure 1). After the first, second, and third surveillance round, 81%, 88%, and 93% of patients were surveilled with an interval of 2 years according to the surveillance protocol, respectively.

AN during follow-up
None of the included patients developed CRC in their retained rectosigmoid during follow-up. Five patients developed AN,
corresponding to a 5-year cumulative incidence of 13% (95% confidence interval [CI] 1.2–23, Figure 2). In 4 out of 5 patients with AN during surveillance (80%), AN was detected in the first round of surveillance; 1 had a TVA, 1 had a dysplastic SP, 2 had SPs ≥10 mm, and 1 patient harbored 3 TSAs. The fifth patient had AN (i.e., a dysplastic SP) during the third round of surveillance (Table 2).

In a sensitivity analysis, we compared patients with and without surveillance before study inclusion. There was no difference in the cumulative 5-year AN incidence between patients who had already received surveillance before study inclusion compared with those who received their first surveillance colonoscopy during the study (10.2% vs 12.9%, log rank \( P = 0.57 \)).

### Ileosigmoidal vs ileorectal anastomosis

Three of the 29 patients (10%) with an ileorectal anastomosis developed AN (10%), compared with 2 of 19 (10.5%) with an ileosigmoidal anastomosis. The hazard of developing AN did not differ between these groups: the 5-year cumulative AN incidence was 11% (95% CI 0.25) for patients with ileosigmoidal anastomosis, compared with 12% (95% CI 0.25) for those with an ileorectal anastomosis (\( P = 0.83 \); see Figure, Supplementary Digital Content 2, http://links.lww.com/AJG/B252).

### Polyps detected during surveillance rounds 1–4

During surveillance rounds 1–4, a total of 124 polyps were removed. Of these, 110 were classified as SP (89%) and 5 as adenoma (4.0%). The 110 SPs consisted of 66 HPs (60%), 24 unspecified SPs (22%), 17 SSLs (15.5%), and 3 TSAs (2.7%). Seven (6.4%) of these were advanced SPs, 56 (51%) were nonadvanced but relevant SPs (i.e., HPs ≥5 mm or SSLs of any size), and 47 (43%) were nonrelevant SPs (i.e., HPs <5 mm). Of the 5 resected adenomas, 4 were classified as tubular adenoma and 1 as TVA.

### Table 2. Findings before and during surveillance

<table>
<thead>
<tr>
<th>Findings during prospective follow-up</th>
<th>Polyps detected during surveillance rounds 1–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>During/before the clearing phase (n = 48)</td>
<td>Surveillance 1 (n = 48)</td>
</tr>
<tr>
<td>Patients with CRC, n (%)</td>
<td>22 (46%)</td>
</tr>
<tr>
<td>Patients with ≥1 polyp, n (%)</td>
<td>48 (100%)</td>
</tr>
<tr>
<td>No. of polyps per patient, median (range)</td>
<td>39 (10–285)</td>
</tr>
<tr>
<td>Patients with ≥1 advanced polypa</td>
<td>41 (85%)</td>
</tr>
<tr>
<td>Patients with at least 1 polyp</td>
<td>48 (100%)</td>
</tr>
<tr>
<td>Any SP</td>
<td>44 (92%)</td>
</tr>
<tr>
<td>HP</td>
<td>42 (88%)</td>
</tr>
<tr>
<td>SSL</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>TSA</td>
<td>32 (67%)</td>
</tr>
<tr>
<td>SP ≥ 10 mm</td>
<td>19 (40%)</td>
</tr>
<tr>
<td>Median no. of SP per patient (range)</td>
<td>Any SP</td>
</tr>
<tr>
<td>HP</td>
<td>12.5 (0–126)</td>
</tr>
<tr>
<td>SSL</td>
<td>11.5 (0–207)</td>
</tr>
<tr>
<td>TSA</td>
<td>0 (0–2)</td>
</tr>
<tr>
<td>SP ≥ 10 mm</td>
<td>2 (0–31)</td>
</tr>
<tr>
<td>SP with dysplasia</td>
<td>0 (0–23)</td>
</tr>
<tr>
<td>Patients with at least 1 adenoma</td>
<td>43 (90%)</td>
</tr>
<tr>
<td>Advanced adenomaa</td>
<td>22 (46%)</td>
</tr>
<tr>
<td>Median no. of adenomas per patient (range)</td>
<td>3 (0–50)</td>
</tr>
<tr>
<td>Advanced adenomab</td>
<td>3 (0–10)</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; HP, hyperplastic polyp; SP, serrated polyp; SSL, sessile serrated lesion; TSA, traditional serrated adenoma.
aAdvanced polyp: advanced adenoma (≥25% villous histology, high-grade dysplasia, ≥10 mm in diameter)/advanced SP (TSA, diameter ≥10 mm, presence of dysplasia).
bAdvanced adenoma: ≥25% villous histology, high-grade dysplasia, and ≥10 mm in diameter.
During each round of surveillance, about half of the patients had one or more polyps removed (Table 2). The yield of advanced polyps was highest during the first round of surveillance (8.3%), whereas only 1 patient developed an advanced polyp during later rounds of surveillance (Table 2 and Figure 3).

DISCUSSION
In this largest prospective cohort study to date, we assessed the yield of endoscopic surveillance in patients with SPS who underwent a (sub)total colectomy. We hypothesized that patients with a little colorectum left in situ would have a limited risk of AN. After a median follow-up of 4.7 years, indeed none of the included patients developed CRC, and AN incidence was low (5-year cumulative incidence 13% [95% CI 1.2%–21%]). All but one AN were found at the first surveillance endoscopy, suggesting an even lower long-term CRC risk after the first round of surveillance. Our results furthermore suggest similar risk of AN for patients with ileosigmoidal and ileorectal anastomosis. Finally, our results show that a large proportion of the detected polyps after a (sub)total colectomy are small HPs. The incidence of relevant lesions such as SSLs or conventional adenomas was low (1,16).

These results confirm that patients with SPS who underwent a (sub)total colectomy are at low risk of AN during surveillance. This contrasts with the high risk of AN in patients without a history of (sub)total colectomy, recently estimated to be over 50% (17). Similar to our results, the same cohort study presented a subgroup analysis of postsurgical surveillance in patients with SPS, in whom AN incidence was much lower than that in patients with SPS who did not undergo a (sub)total colectomy (17).

In our subgroup analysis of ileorectal vs ileosigmoidal anastomosis, we found no difference in terms of AN risk during follow-up. Although compromised by the small size of these subgroups (29 and 19 patients, respectively), this is an important finding, as a longer bowel segment in situ may help to achieve better postoperative bowel function. Previous studies suggested that a postsurgical rectosigmoid length of ≥20 cm was needed for a patient to acquire satisfactory postoperative bowel function (18), and ileosigmoidal anastomosis has been linked to superior postoperative bowel function compared with ileorectal anastomosis (19). Therefore, if (sub)total colectomy is indicated for patients with SPS, it seems preferable to create an ileosigmoidal anastomosis and leave a segment of the rectosigmoid of at least 20 cm in situ.

Given the prophylactic effect of (sub)total colectomy on CRC in patients with SPS, some might argue that surgery should have a more prominent place in the standard treatment of SPS. However, these benefits have to be weighed against the inherent risk of surgery-related morbidity and mortality. In the modern era of minimal invasive surgery, perioperative morbidity after colorectal surgery has been reduced substantially, and mortality rates are low. In a recent cohort study of elective laparoscopic colorectal surgery in the Netherlands, mortality and morbidity rates were 2.4% and 19%, respectively, which was substantially lower than those after open colorectal surgery (20). Furthermore, functional outcome after laparoscopic (sub)total colectomy, particularly in patients with ileosigmoidal anastomosis, is good (19). Nevertheless, morbidity rates after surgery still exceed the risk of morbidity after endoscopic management of SPS, and functional outcomes are not jeopardized when SPS is managed endoscopically (4,9). Hence, despite its
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ect on CRC risk, we believe that prophylactic (sub)total colectomy should not serve as a standard treatment of SPS, but be reserved for patients with exceptional polyp burden, CRC, or endoscopically unresectable polyps. The potential benefits and risks of surgery vs multiple endoscopic interventions should be weighed in shared decision with each patient (21).

Although our study was not designed to evaluate the optimal surveillance interval, we think our results give reason to believe that the currently recommended interval of 1–2 years might be too stringent, given the relatively low incidence of AN. Although extension of surveillance intervals should be performed with caution and as part of prospective cohort studies, we propose a concept for a surveillance strategy, which includes the aforementioned recommendation to preserve a longer segment of the rectosigmoid and extended surveillance intervals up to 5 years (Figure 4). Because the yield of AN was highest during the first round of surveillance, we propose that the first surveillance takes place 1 year after the clearing phase. In case of no AN and less than 5 nonadvanced polyps are detected during any round of surveillance, intervals can be extended to 3 and then to 5 years (Figure 4). Before implementation in clinical practice, this proposed surveillance strategy should be evaluated empirically.

We believe our study has several strengths. First, this was the largest study to date assessing the risk of CRC and AN during follow-up in patients with SPS after a total or (sub)total colectomy. All endoscopies were performed in centers with years-long experience in the management of SPS and were routinely performed on dedicated endoscopy programs. Second, all patients were surveilled with the same surveillance protocol, eliminating the potential bias of varying surveillance intervals. Several limitations have to be acknowledged as well. Some clinicians in participating centers indicated that they regarded SPS patients with a history of (sub)total colectomy as a group of low-risk patients and, therefore, deviated from the study protocol, extending surveillance intervals to 3 or 5 years, in some patients. Although we were aware of only 2 of such cases (Figure 1), we cannot rule out that more patients were excluded for this reason, which might have resulted in a selection bias. Second, patients with an ileorectal anastomosis underwent more extensive surgery than those with ileosigmoidal anastomosis, and hence, they might have harbored a more severe SPS phenotype than patients with ileosigmoidal anastomosis at baseline. However, in a sensitivity analysis, both groups had similar incidence of CRC (P = 0.72) and harbored a similar number of advanced polyps before their (sub)total colectomy (P = 0.50). Third, some patients already received endoscopic surveillance before inclusion, whereas others did not. These 2 groups might theoretically differ in their risk of AN during our prospective follow-up. However, in a sensitivity analyses, there was no difference in AN incidence in patients with compared to patients without surveillance before study inclusion (logrank P = 0.571). Fourth, in our subgroup analysis of ileorectal vs ileosigmoidal anastomosis, our sample size was relatively small (29 vs 19 patients, respectively) and was not sufficiently powered to detect subtle differences in AN between ileorectal and ileosigmoidal anastomosis. Last, we could not report on the use of (virtual) chromoendoscopy for surveillance because this information was not systematically reported. The proportion of colonoscopies that were performed with pancolonic (virtual) chromoendoscopy is likely to be small because neither is routinely used in SPS management in the participating centers.
Nevertheless, cross-national and cross-center differences in the use of such modalities could have potentially influenced our results because a recent study showed that chromoendoscopy might result in slightly higher detection of polyps in patients with SPS (21). However, most of the additionally detected polyps in this study concerned small serrated lesions rather than AN (21).

In conclusion, much of the excess CRC risk in patients with SPS is mitigated by (sub)total colectomy. Based on the low AN incidence in these patients, we propose extension of surveillance intervals, which we incorporated in a newly proposed surveillance strategy (Figure 4). Such extension of surveillance should be performed with caution in experienced centers and preferably as part of high-quality prospective cohort studies. Last, ileosigmoidal anastomosis seems to result in the same AN risk as ileorectal anastomosis. Considering the beneficial outcome after ileosigmoidal anastomosis and a retained rectosigmoid length of ≥20 cm (18,19), surgeons and gastroenterologists should make a joint effort to preserve a maximum length of the retained rectosigmoid.

**CONFLICTS OF INTEREST**

Guarantor of the article: E. Dekker, MD, PhD.

Specific author contributions: F. Balague and E. Dekker shared senior authorship. Conception and design: A.B., J.J, and E.D. Data acquisition: all authors. Data analysis and interpretation: all authors. Drafting the manuscript: A.B. Critical revision of the manuscript: all authors. Statistical analyses: A.B.

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Potential competing interests: E.D. has endoscopic equipment on loan of FujiFilm; received a research grant from FujiFilm, Tillots, and Olympus; and received a speakers’ fee from Olympus and Roche. F.B. has endoscopic equipment on loan of Fujifilm; received an honorarium for consultancy from Fujifilm, Tillots, and Olympus; and received a research grant from Fujifilm; received an honorarium for consultancy from Sysmex; and received a speakers’ fee from Norgine. M.P. received a research grant from Fujifilm; received a consultancy fee from Norgine; and received a speakers’ fee from Olympus, Norgine, Casen Recordati, and Janssen. The other authors have nothing to disclose.

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