

Reducing the polyp burden in serrated polyposis by serial colonoscopy: the impact of nationally coordinated community surveillance

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ABSTRACT

BACKGROUND: Serrated polyposis syndrome (SPS) is associated with an increased risk of colorectal cancer (CRC) and an evolving management approach. The aims of this study were to assess the polyp burden reduction over time, and the incidence of CRC in serrated polyposis patients undergoing community surveillance.

METHODS: This is an observational study based on prospectively collected data. A total of 96 SPS patients with no personal history of CRC were prospectively enrolled in a surveillance program under the guidance of a tertiary center. Patients underwent surveillance colonoscopy in multiple centres across New Zealand.

RESULTS: Patients underwent a median of four colonoscopies with a median interval of 15 months over a median follow-up period of 4.8 years. Five of 96 patients (5%) were referred for surgery, and the remaining 91 were managed by colonoscopy alone. In patients referred for surgery, 92% of the surveillance intervals to the fourth colonoscopy had been ≤ 12 months compared to 33% ($P < 0.001$) in the colonoscopy only group, and all five (100%) had ≥ 20 pancolonial polyps after four procedures compared with only 5/91 (5%) in those managed by colonoscopy alone. In patients successfully managed by colonoscopy, 86% had < 10 pancolonial polyps, $> 75\%$ no longer had polyps ≥ 10 mm and $> 90\%$ no longer had proximal serrated polyps ≥ 10 mm after the fourth colonoscopy. No patients were found to develop CRC during the study time period.

CONCLUSIONS: Patients with SPS were managed by proactive surveillance colonoscopy in wider hospital settings under tertiary centre guidance, with only 5% requiring surgical management. No CRC was diagnosed in any patient during surveillance.

Serrated polyposis syndrome (SPS), formerly known as hyperplastic polyposis, is a disorder of unknown aetiology, characterised by the occurrence of multiple serrated polyps in the large bowel and an increased risk of colorectal cancer (CRC) for affected individuals and their relatives.¹⁻⁴ The prevalence of SPS in the general population is currently unknown and is thought to be underestimated.^{5,6} There are evolving views on what is considered the optimal management for individuals with SPS. For

endoscopists undertaking colonoscopic surveillance the major concern is the reported occurrence of CRC despite the colonoscopy interval being one to two years.⁷ It is unknown whether this represents sub-optimal control of polyp numbers, a high 'miss rate' in the proximal colon, or rapid malignant transformation of advanced serrated polyps *per se*.⁷⁻⁹

Current guidelines recommend that SPS patients should be offered yearly colo-

scopic surveillance with intent to clear the proximal colon of all polyps, or at a minimum all polyps ≥ 5 mm in size if there are numerous diminutive lesions. Surgery is advised if endoscopic control of polyps is not feasible.¹⁰ However, there is limited information on the time frame and residual polyp burden that defines failed or failing endoscopic control. The aims of this study were 1) to record the polyp burden over time and the incidence of CRC in SPS patients who were participating in a community colonoscopic surveillance program with tertiary center guidance, and 2) to identify characteristics of patients who mandated prophylactic colorectal surgery as part of their management.

Methods

Study cohort

Patients from urban and regional areas throughout New Zealand with suspected SPS, regardless of whether there was a family history of CRC, were referred by colonoscopists (either gastroenterologists or surgeons) to the New Zealand Familial Gastrointestinal Cancer Service (NZFGICS), a national multidisciplinary tertiary service with longstanding expertise in the diagnosis and management of familial gastrointestinal polyp and cancer syndromes. Referral was made to request ongoing management recommendations regarding colonoscopy surveillance intervals or surgery in their patient with SPS and colonoscopic surveillance advice for first-degree relatives. Those with a confirmed diagnosis of SPS were prospectively offered enrolment in the Genetics of Serrated Neoplasia (GSN) study from 2000 to 2014. For inclusion in the study, patients had to meet the World Health Organization (WHO) criterion 1 (at least five histologically confirmed serrated polyps proximal to the sigmoid colon, with two or more of these being > 10 mm) and/or criterion 3 (> 20 serrated polyps of any size but distributed throughout the colon) for SPS,³ as these two criteria are relevant to control of polyp burden.¹¹ Exclusion criteria covered patients with known or suspected Lynch syndrome, known to be *APC* or bi-allelic *MUTYH* mutation carriers, and patients with a previous history of colorectal surgery due to 1) colorectal cancer or 2) conditions other than CRC. Patients gave

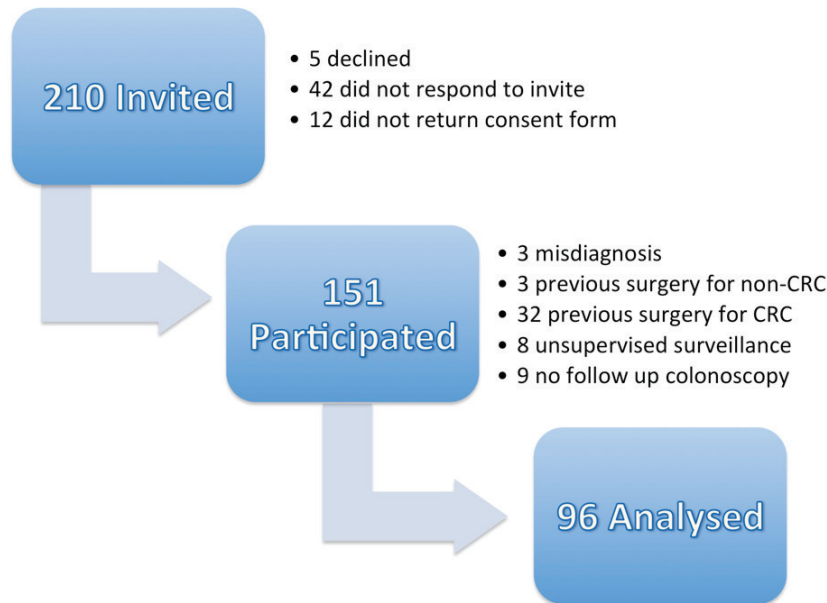
written informed consent to participate in research (HDEC of NZ Protocol NTX 08/03/013). Patients who declined participation in the study were offered identical clinical management recommendations by the tertiary service.

Study design and data collection

The NZFGICS clinical advisors (gastroenterologists or colorectal surgeons) reviewed the colonoscopy and histology reports after each procedure, and the referring clinician and patient were given prospective management recommendations. Following the management recommendations, colonoscopies continued to be performed by the referring specialists within 31 public or private hospital endoscopy units. For a subset of the patients (27%) NZFGICS specialists performed the procedures in their hospital practice. At each surveillance procedure, the aim was to complete examination to the caecum and ensure that all visible polyps proximal to the sigmoid colon were removed with < 10 polyps (≤ 5 mm in size) remaining in the distal colorectum. Surveillance was recommended at 12–18 month intervals, with initial earlier repeat procedures at intervals of 12 months or less if the aims for polyp control were not being achieved, there was evidence of incomplete polyp removal or there was poor bowel preparation. Colectomy with ileo-rectal anastomosis was recommended for non-resectable large polyps and/or recurring numerous polyps. Patients who went to surgery were censored at time of surgery for the follow-up analysis.

Each colonoscopist documented the number, size and location of polyps at each procedure, and these were linked to the corresponding histology report. Polyps were classified into conventional adenomas and hyperplastic/serrated polyps. All subtypes of serrated polyps, as defined by the WHO,³ were grouped as a single entity and considered by size ($<$ or ≥ 10 mm) and site (proximal or distal colon). The proximal colon included the caecum, ascending colon and transverse colon. As far as possible, polyp counts were estimated from colonoscopy reports. Where reports documented ranges in polyp numbers or reported, for example greater than 20 polyps, the lower number was recorded.

Figure 1: Triage of patients invited to participate in the Genetics of Serrated Neoplasia study (n=210).



Fifty-nine patients did not participate (28%). Thirty-two patients (15%) had previous surgery for CRC. Previous surgery for non-CRC (n=3) describes three patients excluded from the intact colons group with no prior CRC who had undergone surgical removal of large tubulovillous adenomas or a carcinoid.

Statistical analysis

Statistical analyses were performed with SPSS statistical software version 23.0 (IBM) and Prism V7. Comparisons were performed using a chi-squared or exact test for categorical variables and a *t*-test for continuous variables. A two-tailed *p*-value was used for comparative analyses and a *p*-value of less than 0.05 was used to determine statistical significance.

Results

Baseline characteristics

A total of 210 SPS patients were invited to participate, and a final 96 were initially included in the study (Figure 1). Patient characteristics are listed in Table 1. Of the participants, six (6%) met WHO criterion 1 only, 23 (24%) met both WHO criteria 1 and 3, and the remaining 70% met WHO criterion 3 only. Thirty patients (31%) in this cohort had been described in previous reports.^{12,13}

Colonoscopies

A total of 335 colonoscopies were reviewed (96 initial and 239 subsequent procedures). A small number of incomplete procedures for poor bowel preparation or technical reasons were not counted in the total. No patient underwent surgical treatment for complications of colonoscopy.

Patients were partitioned into those who were referred for prophylactic colectomy (n=5) and those who remained on colonoscopy surveillance (n=91). In patients referred for colectomy, only procedures prior to surgery were included in the analysis. Of all patients studied, 28 had two, 22 had three, 27 had four and 19 had five or more procedures. Surveillance characteristics for each group are presented in Table 2 and numbers of colonoscopies analysed are shown in Figure 2.

Polyp features

The polyp features across serial procedures are illustrated in Figure 3. An average pan-colonic serrated polyp count of <10 was documented after four colonoscopies for patients who were not referred for surgery (n=91), with only 14% (13/91) of these patients having individual polyp counts of ≥10 at this procedure. In contrast, in patients who underwent prophylactic colectomy (n=5) the average pan-colonic serrated polyp count remained at 20 or greater throughout four procedures (Figure 3a). Overall, >75% of patients managed by colonoscopy no longer have polyps ≥10mm in size at the fourth colonoscopy. However, at least one polyp of any size was still present in the proximal colon in at least 80% of all patients (Figure 3b). Large (≥10mm) serrated polyps

Table 1: Patient details and baseline polyp features of serrated polyposis patients.

	All patients n=96	Colonoscopy surveillance n=91	Prophylactic surgery n=5	P-value *
Median age at diagnosis (IQR) years	48 (33–59)	44 (32–59)	54 (53–64)	
Patients (females)	96 (60)	91 (54)	5 (4)	0.65
Ever smoker (%)	58 (60)	54 (59)	4 (80)	0.65
Current smoker (%)	19 (20)	18 (20)	1 (20)	0.99
Family history CRC (FDR, SDR) (%)	56 (58)	53 (58)	3 (60)	0.99
First-degree family history of CRC (%)	19 (20)	18 (20)	1 (20)	0.99
WHO Criterion 3 (%)	90 (94)	85 (94)	5 (100)	0.99
Polyps >10mm (%)	61 (64)	58 (64)	3 (60)	0.99
Proximal polyps >10mm (%)	46 (48)	43 (48)	3 (60)	0.99
Serrated polyps >10mm (%)	53 (55)	50 (57)	3 (60)	0.97
Proximal serrated Polyps >10mm (%)	42 (44)	39 (43)	3 (60)	0.65
Any conventional adenoma (%)	59 (61)	55 (60)	4 (80)	0.65
Advanced adenoma# (%)	13 (14)	12 (13)	1 (20)	0.99

* Colonoscopy only surveillance group vs prophylactic surgery.
 #Advanced adenoma includes those with high-grade dysplasia, villous histology and size 10mm or greater.
 FDR = first-degree relative.
 SDR = second degree relative.
 IQR = interquartile range.

Figure 2: Graphical representation of numbers of patients who underwent two, three, four and five or more colonoscopies.

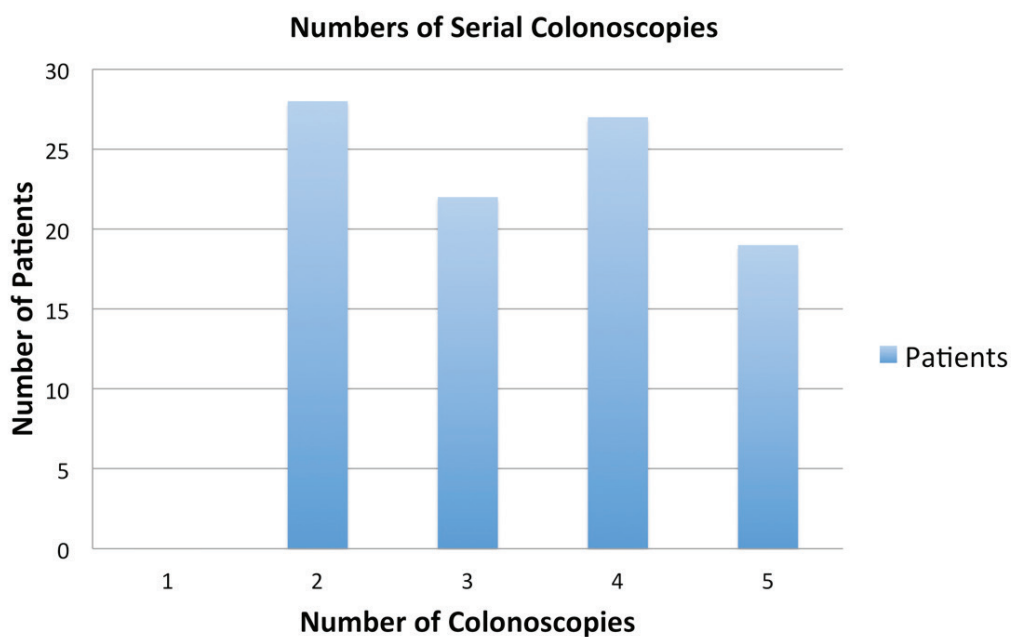
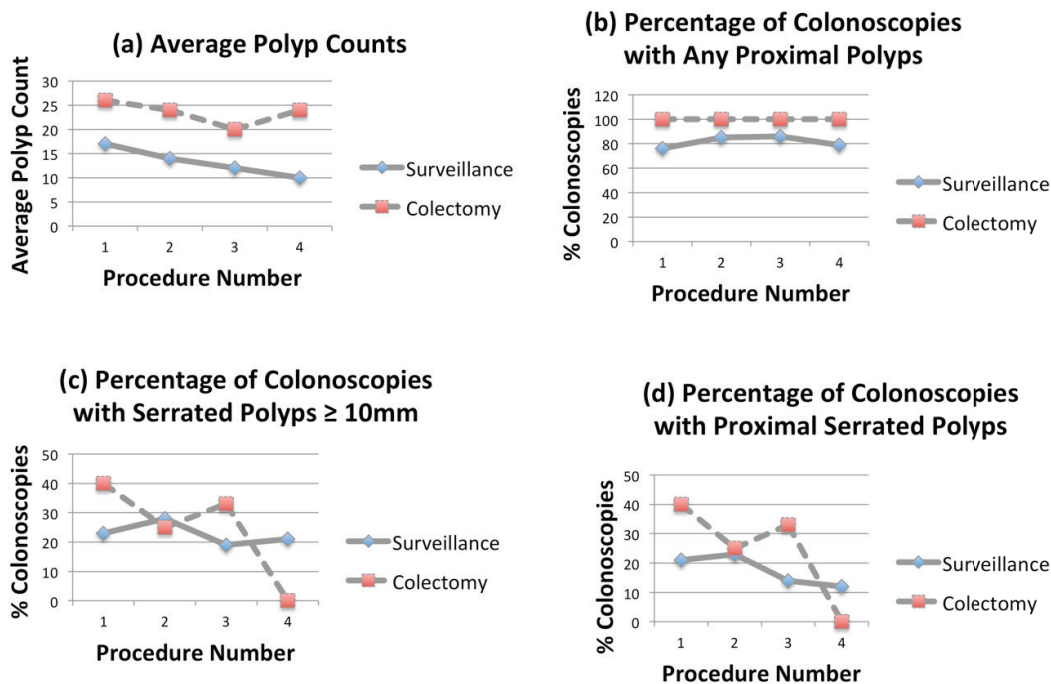


Table 2: Surveillance characteristics of each patient group.

	All patients	Colonoscopy surveillance	Prophylactic colectomy	P-value
Median follow-up (IQR) years	3.6 (1.4–7.2)	3.7 (1.8–7.3)	2.7 (1.0–4.4)	
Median interval colonoscopy: (IQR) months	16 (11–31)	17 (12–32)	10 (7–13)	
No of intervals 12 months or less	85/237 (36%)	74/223 (33%)	11/13 (85%)	P<0.001*
Interval CRC	0	0	0	

Colonoscopy-only group vs colectomy group.
IQR = interquartile range.

Figure 3: Colorectal polyps identified during serial surveillance procedures in patients managed by colonoscopy only (solid line) and patients who subsequently underwent prophylactic colectomy (dashed line).

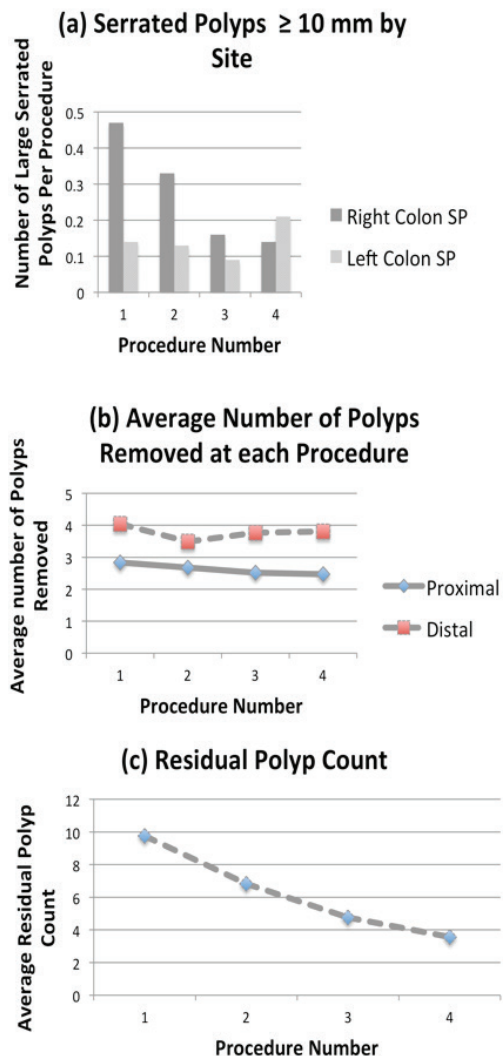


- a) average polyp count at each colonoscopy procedure
- b) polyps of any size were still detected in the proximal colon in the majority of patients at the fourth colonoscopy
- c) large serrated polyps 10mm or greater in size were still developing in 20% of patients at the fourth colonoscopy
- d) large proximal serrated polyps 10mm or greater in size were still documented in the right colon in 11% of patients at the fourth colonoscopy.

Surveillance = patients with intact colons

Colectomy = patients with intact colons who underwent a colectomy.

Figure 4: Colorectal polyps removed and those remaining after a procedure.



- a) proximal large serrated polyps decreased markedly over time, despite similar rates of polyp removal in both segments of the colon,
- b) the average number of polyps removed from both the proximal and distal colon at each procedure remained steady and
- c) estimated residual polyp count also decreased over time in the patients with intact colons.

were present anywhere in the colon in 20% of patients (Figure 3c), and in the right colon in 11% of patients (Figure 3d) at the fourth procedure.

Individual polyp counts at each serial procedure are depicted in Figure 4a, and

median counts for serial procedures are shown in Figure 4b, with decreasing total numbers of polyps seen over time. In contrast, Figure 4c shows no similar trend, with individual polyp counts remaining above 10.

Though serrated polyps continued to be found in the proximal colon at similar levels over time, importantly, the number of serrated lesions ≥10 mm declined sharply over four serial procedures (Figure 4a). The average number of polyps removed at each procedure in the proximal and distal colon was consistent over time, and is shown in Figure 4b. An estimate of the number of polyps remaining at the end of the procedure decreased over time from an average of 10 polyps at the first colonoscopy to an average of four polyps at the fourth colonoscopy (Figure 4c). No CRC was diagnosed in any of the patients during surveillance.

Prophylactic colectomy patients

Five patients (four females) were referred for surgery. Multiple factors prompted referral for surgery. Failure to satisfactorily control the polyp burden, despite short intervals between colonoscopy procedures, was the overlapping reason for surgical referral in all five. In addition, three of the five patients *also* had polyps >20mm in size that were considered technically difficult to remove endoscopically, one had advanced histology (focal high-grade dysplasia) and the colonoscopy procedure itself was technically difficult for another. No CRC was identified in any of these five patients, three of whom met both WHO criteria, compared with 20/91 (22%) of patients managed by colonoscopy alone (p=0.07). The majority of surveillance intervals in the group referred for surgery were 12 months or less (11/13 or 85%) compared with those within the group who did not go to surgery (74/223 or 33%; P<0.001). Of interest, 5/91 patients from the group who did not go to surgery (5%) demonstrated >20 polyps at fourth colonoscopy. These patients, however, also had significantly fewer short surveillance intervals (12 months or less) than those patients who were referred for surgery (6/15 or 40% vs 11/13 or 85%) (p=0.023).

Discussion

This study was undertaken to evaluate the efficacy of a monitored surveillance colonoscopy program to obtain control of polyps and prevent CRC in SPS patients. To date, data informing current best practice recommendations^{7,14} have emerged out of tertiary single-centre surveillance programmes. However, it is inevitable that SPS patients, as in our study, will have colonoscopy surveillance performed by a number of different specialists with a range of expertise in varied endoscopy unit settings. In this study, colonoscopy surveillance was co-ordinated by a national tertiary service (the NZFGICS), thereby representing a more 'real world' setting. Our results demonstrate that, at the fourth colonoscopy procedure, surveillance with tertiary centre guidance in SPS patients with intact colons is associated with 1) a reduction in the average pan-colonic serrated polyp burden to less than 10 polyps, 2) the elimination of large polyps (≥ 10 mm in size) overall in the majority (75%) of patients, especially in the right colon (almost 90% of patients), 3) the persistence/recrudescence of small polyps and 4) the necessity of referral for prophylactic colectomy in only the minority (5%) of patients. None of the patients in this study developed CRC.

For patients managed by colonoscopy alone [33% of the intervals between colonoscopy procedures were ≤ 12 months], the average polyp count, including small distal lesions, was ≤ 10 at the fourth procedure. In contrast, for patients who subsequently underwent prophylactic colectomy, despite the majority (85%) having short intervals (≤ 12 months) between colonoscopy procedures, the average pan-colonic polyp count remained at > 20 . This reflected the chief reason for proceeding to surgery, namely endoscopic failure to control the polyp burden. The consideration here was not only the (unknown) cancer risk, but also the higher risk of complications from frequent multiple polypectomies. For those patients in whom polyp burden was reduced successfully, and who show no high-risk features, our results suggest the colonoscopy interval could be safely increased beyond 12 months. This possibility is supported by a recent editorial, which argues for tailoring surveillance interval to risk stratification in serrated polyposis patients.¹¹

Persisting polyps

Our study shows that small proximal serrated polyps continue to be observed despite surveillance, and that in a small subset of patients, large proximal serrated polyps will be seen at the fourth colonoscopy. This finding has previously been described⁷ and may reflect variability of detection of proximal serrated lesions by gastroenterologists in different endoscopy centres.⁹ As most serrated polyps are sessile and subtle in appearance, factors besides bowel preparation, such as withdrawal time and thoroughness of examination, are likely to influence their detection.¹⁵ Therefore, the perception of development of new polyps during the surveillance interval may (in part) be due to the growth of previously missed lesions.

Risk predictors of CRC

High-risk features which predict CRC in serrated polyposis have been reported previously.^{16,17} IJ Speert and colleagues have reported that the risk factors for CRC in the SPS setting include the presence of at least one dysplastic serrated polyp, the presence of an advanced adenoma and the concurrent presence of WHO criteria 1 and 3.¹⁷ Counter-intuitively, there is evidence that not all CRC in the setting of multiple serrated polyps arise from advanced serrated lesions,¹³ and the proportion of large serrated polyps themselves, which undergo malignant transformation if left *in situ*, is not reliably known.^{18,19} Therefore, predicting which SPS patients are at the highest risk for CRC continues to present difficulties, particularly as surveillance modifies the natural history. This has led to the emerging and encouraging perception that the risk of CRC in SPS patients under surveillance is relatively low.²⁰ It should be noted that the five patients in our study who underwent prophylactic colectomy had revealed no evidence of malignancy. The possibility that appropriate surveillance may prevent CRC from occurring even in the presence of high-risk features may therefore exist.

Incidence of CRC in SPS

The absence of CRC development in our study raises the question that CRC incidence in this SPS subgroup is lower than thought. This is concordant with the view that patients who develop CRC in SPS are diagnosed either synchronously with SPS

or during follow-up colonoscopy after surgery for the CRC.²¹ This detection bias could contribute to the (high) reported CRC incidence in SPS.¹¹ Two comparable earlier, though retrospective, studies reported CRC rates of 7% in SPS patients undergoing surveillance.^{1,7} However, they differ in not proactively removing all polyps, and the surveillance intervals were extended beyond those currently recommended. In mitigation, the time period of the Netherlands study (May 1982 to June 2008) overlapped the time before SPS was widely recognised (mid-1990s), and this would have impacted the policy on polyp removal and colonoscopy surveillance. In the other study from the US,⁷ a longer median interval (2.0 years) was followed for patients under surveillance between the years 2001 and 2010, compared with 1.4 years in our study over a similar time period (2000–2014). However, due to intense local interest^{22,23} SPS was well recognised and reported in New Zealand, with early dissemination of a management protocol promoting a shorter colonoscopy interval with a proactive approach to achieving polyp clearance. This may in part be responsible for the absence of CRC observed in our study, and now being confirmed by others.^{14,24}

Surgical intervention

The above-mentioned low rate of surgical referral for polyposis management during the 14-year study period under our protocol is an important finding. In contrast, the US study reported 27% of patients being managed with surgery.⁷ More recently, a study from the Netherlands reported that 25% of patients were referred for surgery.¹⁷ Despite our lower rate of surgical intervention (5%), and 23 patients meeting both WHO criteria 1 and 3, a known risk factor for CRC, no patient developed CRC. This question of possible surgical over-treatment has to be considered, and more work is needed to better identify those patients most at risk for CRC.

Limitations

This study has a number of limitations related to its historical contexts and setting. Data on colonoscopy quality performance indicators were not available, although this was also the case in two previous reports

which have contributed to the current knowledge base regarding this disorder.^{1,7} However, all colonoscopy reports were reviewed by an NZFGICS specialist and flagged if there was any concern that the procedure was incomplete, satisfactory polyp control not achieved, incomplete polyp removal noted or bowel preparation reported as poor. This resulted in recommendations for an early repeat procedure being made, and alerts created to ensure the resultant procedure report were reviewed.

Another limitation was that there was no documentation of whether or not enhanced imaging techniques were used in polyp detection at colonoscopy. This is mitigated in the light of a recent publication report that narrow band imaging does not reduce polyp miss rates in patients with SPS.²⁵

The histological criteria for the diagnosis of serrated polyps evolved over the time of the study. No centralised retrospective histology review was performed, and polyps were only categorised by site, size and histology (serrated/hyperplastic polyps or conventional adenomas), with information on dysplasia in serrated lesions not available. Therefore, we did not separately analyse the different subtypes of serrated polyps, in particular separating hyperplastic polyps from sessile serrated adenomas. Nevertheless, the separation of serrated polyp type by size and location could be considered as surrogate markers for advanced serrated lesions. This is a reasonable strategy, bearing in mind that the current WHO definition of serrated polyposis is based on the presence of histologically confirmed serrated polyps of threshold numbers and sizes, and not on serrated polyp subtype.

Ascertainment bias is possible, as the majority of patients in this study were referred for management of polyposis and therefore met WHO criterion 3, and thus the findings of our study are likely more relevant to SPS patients with higher polyp numbers. Further limitations include median colonoscopy intervals masking the shorter intervals required initially to control the polyp burden, as well as the longer intervals where patients failed to adhere to the recommended protocol.

Summary

In our study we observed that, under our community approach, only 5% of patients required referral for surgery, and no participant required surgical intervention for an adverse procedure-related outcome. In the majority of these patients, reduction of the average pan-colonic polyp burden to <10, the absence of polyps ≥ 10 mm in size in 75%, and the absence of proximal serrated polyps ≥ 10 mm in size in 90% of patients at the fourth procedure, was

achievable if colonoscopy was performed at intervals appropriate to the polyp burden.¹¹ Importantly, no CRC events were observed under this regimen of tertiary monitored community surveillance, a model which reflects real world practice. These findings support the general guidelines set out by the US Multi-Society Task Force on Colorectal Cancer,²⁶ which suggest yearly colonoscopic surveillance of SPS patients and the recently proposed algorithm of risk-stratified management of patients with SPS.¹¹

Competing interests:

Dr Burt reports personal fees from Thetis Pharma outside the submitted work.

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