The clinical significance and synchronous polyp burden of large (≥ 20 mm) sessile serrated polyps in patients without serrated polyposis syndrome

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Methods
Patients with at least one SSP (≥ 20 mm) were eligible. Data from three consecutive colonoscopies were used to compare clinical and endoscopic characteristics in three patient groups: SPS, a solitary large SSP, and patients with at least two SSPs without fulfilling the criteria for SPS (oligo-SSP). Data on the diagnostic colonoscopy were collected retrospectively, whereas the remaining data was collected prospectively.

Results
67/146 patients (45.9%) had SPS, 53/146 (36.3%) had a solitary SSP, and 26/146 (17.8%) were categorized as oligo-SSP. Personal (16.4 %, 9.4 %, and 11.5 %, respectively) and family (17.9%, 17.0 %, and 23.1 %, respectively) history of colorectal carcinoma did not differ significantly between groups. Polyp burden was greater in SPS compared with solitary SSP but was not different from oligo-SSP (advanced adenomas: SPS 32.8 % vs. solitary SSP 9.4 % [P=0.002] vs. oligo-SSP 34.6 % [P=0.87]; ≥ 10 conventional adenomas: 11.9 % vs. 0 % [P=0.01] vs. 3.8 % [P=0.44], respectively). Dysplasia in large SSPs was frequent in all groups (41.1 % overall). SPS was recognized by referring endoscopists in only 9.0 % of cases.

Conclusion
Patients with oligo-SSPs have similar synchronous polyp burden and clinical characteristics as patients with SPS and may require similar surveillance. Modification of the criteria for the diagnosis of SPS to include this group seems warranted. Patients with a solitary SSP have a lower risk of synchronous polyps, including advanced adenomas. Larger studies are warranted to determine whether these patients may return to standard surveillance following complete examination and clearance of the colon.
lining the importance of their recognition and complete endoscopic removal.

SSPs can occur sporadically or as part of the serrated polyposis syndrome (SPS). SPS represents a heterogeneous group of phenotypes and is currently defined by the World Health Organization (WHO) as having one of the following features: at least five serrated polyps located proximally to the sigmoid colon, two of which are >10 mm in diameter (type 1); any number of serrated polyps located proximally to the sigmoid colon in an individual who has a first-degree relative with SPS (type 2); or at least 20 serrated polyps of any size distributed throughout the colon (type 3) [13].

Whereas it is known that an increasing number of SSPs in SPS is associated with the development of CRC [14] and that annual colonoscopic surveillance of patients with SPS reduces their risk of CRC [15], the clinical significance of large SSPs (≥20 mm) outside the definition of SPS is less well studied. A strong association has been described between proximal and SSPs ≥10 mm, respectively, and synchronous advanced neoplasia in a screening population [5, 10, 11, 16–18], and therefore their role in the development of CRC seems to be important. In addition, CRC diagnosed within 5 years after a colonoscopy is significantly more likely to be positive for CpG island methylator phenotype and microsatellite instability compared with CRC diagnosed 5 years after colonoscopy or in colonoscopy-naive patients [19]. Recently, the risk of CRC in patients with serrated polyps who do not meet the criteria for SPS, and the risk for their first-degree relatives, has been shown to be similar to the risk in patients with SPS [20]. Based on this evidence, we hypothesize that patients with sporadic large SSPs may have distinct characteristics necessitating separate surveillance guidelines compared with those who have conventional adenomas.

The aim of the current study was to characterize the clinical features and synchronous polyp burden of patients with at least one large SSP, and to classify such lesions according to whether they fulfill the WHO definition of SPS.

**Methods**

**Patients and data collection**

Participants were identified from a cohort of patients who were referred to a single Australian tertiary center for endoscopic removal of large laterally spreading lesions (LSL, ≥20 mm) as part of the multicenter Australian Colonic Endoscopic Resection study between September 2008 and June 2017 (NCT01368289). All lesions were initially identified and referred by a nationally accredited endoscopist. Institutional review board approval was obtained. Written informed consent was obtained from each patient.

Patients with at least one large histologically proven SSP who had undergone three colonoscopic procedures during the study period (see below) were eligible. A large SSP was defined as ≥20 mm in maximum dimension. Data were collected from each patient from three successive colonoscopies: the diagnostic procedure performed by the referring endoscopist, the index procedure performed at the tertiary centre, and the first surveillance colonoscopy. The maximum interval between the diagnostic procedure and the index procedure was 3 months. The desired interval between the index procedure at the tertiary centre and the first surveillance colonoscopy was 4–6 months. The maximum time from the diagnostic procedure to the first surveillance colonoscopy was 1 year.

All data from the diagnostic procedure were obtained by retrospective review of the referring colonoscopy and histology report, and included the number and size of synchronous polyps, as described in endoscopy reports, and their histology. The personal and family history of CRC (i.e., one or more first-degree relatives affected) was obtained directly from the patient or from the patient’s referral letter. All other data were collected prospectively, and included patient demographics, large SSP morphology, Paris classification, location, histology, and procedural details.

All SSPs were considered for endoscopic mucosal resection (EMR) at the tertiary center. Split-dose bowel preparation was used for all these procedures. Antiplatelet or anticoagulant agents were ceased prior to the EMR procedure, according to current guidelines [21]. Patients were sedated using intravenously administered midazolam, fentanyl, and propofol. An experienced endoscopist, or an advanced endoscopy fellow under their direct supervision, performed all EMR procedures using Olympus 180 or 190 series high definition, variable-stiffness colonoscopes (180/190 PCF/CF; Olympus, Tokyo, Japan). A standardized inject and resect EMR technique was used, as previously described in detail [22].

All resected specimens were examined by expert gastrointestinal pathologists. All SSPs with dysplasia were re-analyzed by an expert gastrointestinal pathologist to confirm the dysplasia. All authors had access to the study data, and reviewed and approved the final manuscript.

**Definitions**

The study period was defined as the time from the diagnostic procedure to the first surveillance colonoscopy. Eligible patients were classified into three groups based on the findings at all three procedures during the study period:

- patients with a solitary SSP ≥20 mm (solitary SSP group);
- patients with SSPs and at least one SSP ≥20 mm;
- patients with at least two SSPs (at least one of which was ≥20 mm) without fulfilling the criteria of SPS (oligo-SSP group).

Patients with a solitary large SSP had no other SSP of any size. The diagnosis of SPS was defined according to the WHO definition [13] and was cumulative, including all polyps from the three procedures. Polyp burden was defined as all of the colonic lesions present in eligible patients with at least one large SSP, including conventional adenomas, sessile serrated polyps, and advanced adenomas, over the study period. Advanced adenomas were defined according to the definition of the American Gastroenterological Association: adenomas with size ≥10 mm, villous histology or high grade dysplasia [23]. All described colonic lesions detected over the study period were assumed to be synchronous – i.e. existing at the time of the diagnostic procedure whether they were detected or not.
Study end points

The primary end points of the study were the clinical characteristics (personal and family history of CRC and synchronous polyp burden (SSP, conventional adenomas, and advanced adenomas) of patients with large (≥20 mm) SSPs. The secondary end point was the recognition of SSPs by the referring physician using the WHO criteria for SSPs.

Statistical analysis

All SSPs analyzed were ≥20 mm, but when there were two or more SSPs ≥20 mm in a single patient in the SSP or oligo-SSP group, only the largest lesion was used for comparisons between lesion and procedural characteristics in order to avoid potential bias associated with correlated observations related to a single patient. All detected lesions were used in the definition of the three groups and to determine the synchronous polyp burden. The group of patients with a solitary SSP and the oligo-SSP group were compared with the SSP group for patient and lesion characteristics and polyp burden.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 23.0 (IBM Corp., Armonk, New York, USA). Mann-Whitney U tests or two-sample t tests were used to test for differences in the distribution of continuous variables. The Pearson chi-squared or Fisher’s exact test was used to test for systematic differences between categorical variables and outcomes. All P values were two sided and were considered significant when <0.05. The lower and upper limits of the 95% confidence interval (CI) were calculated for a proportion of individuals with any conventional adenoma, advanced adenoma, or colorectal carcinoma. These results were compared with prevalences in an average-risk screening population [24].

Results

Description of the cohort

Between September 2008 and January 2017, 1703 LSLs ≥20 mm were referred for endoscopic resection. A total of 1609 LSLs underwent an attempt at EMR, and 260 (16.2%; 190 patients) of these were excluded histologically to be large SSPs. Overall, 70/260 lesions (23.6%) in 44/190 patients (23.2%) were excluded, as they could not be assessed for polyp burden owing to inadequate referring report (2/44), incomplete first surveillance colonoscopy data (33/44), or because the patient underwent surgery (9/44). A total of 190 lesions in 146 patients were included in the analysis, and 44 patients had more than one large SSP (► Fig. 1).

A total of 67/146 patients (45.9%) had SSPs, 53/146 (36.3%) had a solitary large (≥20 mm) SSP, and 26/146 (17.8%) were categorized as oligo-SSP (at least two SSPs, at least one of which was ≥20 mm, without fulfilling the criteria of SSPs). In the latter group, 14/26 patients had two SSPs, 9 had three SSPs, 2 had four SSPs, and 1 had seven SSPs. In the SSP group, 60 patients were classified as WHO type 1 SSP, none as WHO type 2 SSP, and 7 patients were classified as WHO type 3 SSP.

Patient and lesion characteristics

Patient demographic details are summarized in ►Table 1. Age, sex, personal or family history of CRC, and personal history of polyps did not differ significantly between the three cohorts. Median time from endoscopic removal of the large SSP to the first surveillance colonoscopy was 5.8 months (range 4.9–8 months). A total of 61/67 patients (91.0%) with SSPs were not recognized to have this disorder by the referring endoscopist, including 23/67 (34.3%) with at least 10 SSPs.

Median lesion size was larger in the SSP group (30 mm, interquartile range [IQR] 25–40 mm) than in the solitary SSP group (25 mm, IQR 20–30 mm; P=0.02) but was similar to that in the oligo-SSP group (30 mm, IQR 25–35 mm; P=0.68). Paris classification did not vary between the cohorts. Fewer lesions were located proximally to the transverse colon in the SSP group (42, 62.7%) compared with the solitary SSP group (41, 77.4%), though this was not statistically significant (P=0.08). A similar number were found in this location in the oligo-SSP group (17, 65.4%; P=0.82 vs. SSP). Submucosal fibrosis within the EMR defect was less commonly found in the SSP group (4, 6.0%) than in patients with a solitary SSP (11, 20.8%; P=0.02), but there was no difference compared with the oligo-SSP group (5, 19.2%; P=0.11) (►Table 1, ►Fig. 2).

Synchronous polyp burden (►Table 2)

A total of 34/67 patients (50.7%, 95%CI 39.1–62.4) with SSPs had at least one conventional adenoma compared with 26/53 (49.1%, 95%CI 36.1–62.1; P=0.85) in the solitary SSP group, and 16/26 (61.5%, 95%CI 42.5–77.6; P=0.35) in the oligo-SSP group. Significantly more patients with SSPs had at least one advanced adenoma (22, 32.8%; 95%CI 22.8–44.8) compared with patients with a solitary SSP (5, 9.4%; 95%CI 4.1–20.3; P=0.002); however, there was no difference compared with the oligo-SSP group (9, 34.6%; 95%CI 19.4–53.8; P=0.87). Eight patients (11.9%) with SSPs had at least 10 conventional adenomas compared with none in the solitary SSP group (P=0.01) and one (3.8%) in the oligo-SSP group (P=0.44). Traditional serrated adenomas were found only in the SSP group (6 [9.0%] vs. none in the solitary SSP group [P=0.03], vs. none in the oligo-SSP group [P=0.18]).

Sessile serrated polyps with dysplasia

The overall percentage of SSPs exhibiting dysplasia on histology was 60/146 (41.1%), of which 32 (53.3%) were located proximally to the transverse colon. Dysplasia was no more common in the SSP group (29, 43.3%) than in the solitary SSP group (21, 39.6%; P=0.63) or the oligo-SSP group (10, 38.5%; P=0.67). The colonic distribution of dysplastic SSPs did not vary significantly between the SSP group and the solitary SSP group (P=0.69) or the oligo-SSP group (P=0.67) (►Table 1, ►Table 3, ►Fig. 3).
Discussion

In this study we investigated the clinical features of two patient groups – those with a solitary large SSP, and those with at least two SSPs including one large SSP, not fulfilling the criteria for SPS (oligo-SSP) – and compared them with an SPS cohort. We demonstrated that patients with a solitary SSP have a significantly higher risk of CRC as well as conventional adenomas compared with an average-risk screening population [24], but a smaller risk of advanced adenoma than patients with SPS. Moreover, patients with oligo-SSP have a similar risk of both ad-
vanced adenoma and CRC as patients with SPS. Table 4 summarizes the key findings of the study.

The genetic abnormalities underlying SPS are still unknown, but patients affected by the syndrome have a lifetime risk of developing CRC of 15% – 29%, and their first-degree relatives have...
a 5-fold increased risk of colon cancer [14, 25, 26]. In the current study, a personal history of CRC showed rates in all groups that were significantly higher than the background population (i.e., 0.7% in the age group ≥ 65 years and 0.1% in the age group < 65 years [24]), and therefore the prognoses for these groups should not be regarded as benign. This may be due to the presence of a significantly larger number of synchronous conventional adenomas and advanced adenomas in our study groups compared with the average-risk screening population, and it seems that patients with an SSP ≥ 20 mm have a predisposition to CRC regardless of syndromic context. A recent large, multicenter study showed that the presence of advanced adenoma is associated with a risk of developing CRC [25]. Whereas patients with a solitary SSP had a significantly lower advanced adenoma burden than patients with SSP and oligo-SSP in the current study, the rates were still surprisingly high. Half of patients with a solitary SSP had at least one conventional adenoma and almost 10% had an advanced adenoma. This contrasts with the 5.7% prevalence of advanced adenoma in an average-risk screening cohort [24]. Even more remarkable is the finding that one-third of patients with SPS and oligo-SSP had an advanced adenoma. This supports the evidence that patients with any number of large SSPs are at risk of having an advanced adenoma and thus developing CRC, although this risk is perhaps lower in patients with a solitary SSP [27].

The group of patients with at least two large SSPs (at least one of which was ≥ 20 mm) without fulfilling the criteria for SPS (oligo-SSP group), had similar clinical characteristics and colonic phenotype to patients with SPS. It is possible that this group is on a continuum with SPS and with longer follow-up this group might fulfill the criteria for SPS. It is also possible that the definition of SPS is deficient here, i.e., patients with a propensity to develop serrated polyps may develop over time but may miss out on the definition of SPS applied over a narrow in-

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**Table 3** Distribution of sessile serrated polyps with dysplasia in the colon.

<table>
<thead>
<tr>
<th></th>
<th>SPS (n=29)</th>
<th>Solitary SSP (n=21)</th>
<th>P</th>
<th>Oligo-SSP† (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic flexure and proximal, n (%)</td>
<td>12 (41.4)</td>
<td>14 (66.7)</td>
<td>0.69</td>
<td>6 (60.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Left colon, n (%)</td>
<td>17 (58.6)</td>
<td>7 (33.3)</td>
<td></td>
<td>4 (40.0)</td>
<td></td>
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</tbody>
</table>

SPS, serrated polyposis syndrome group; SSP, sessile serrated polyp group. P values represent comparisons with the SPS group.

† Patients with at least two SSPs (at least one of which was ≥ 20 mm) without fulfilling the criteria of SPS.

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**Fig. 3** Sessile serrated polyps with dysplasia.  
**a**–**c** High definition white-light imaging.  
**d**–**f** Narrow-band imaging (dysplasia within dotted circles).
terval of time. This suggests that oligo-SSP and SPS should be regarded as similar disorders and should undergo colonoscopic surveillance at similar intervals. These findings are supported by a recent study by Egoavil et al. [20]. In contrast, patients with a solitary large SSP appear to belong to a lower risk group. These patients should be treated with caution and counseled regarding controllable risk factors; however, once a solitary large SSP has been removed, and endoscopic surveillance has confirmed the absence of recurrence and no evidence of other large SSP or advanced adenoma, it may be possible to offer these patients surveillance in keeping with conventional guidelines. Further research in this area is needed, although the true group with SPS is likely to be revealed only by elucidation of the specific genetic defects responsible.

Recent developments at the molecular level highlight the importance of dysplasia within SSPs as a harbinger of CRC and the long dwell time of nondysplastic SSPs [28]. The rate of dysplasia within SSPs in the published literature is approximately 14 % [8, 29]. In this enriched cohort, the rate of dysplasia within large SSPs was high (around 45 %) and similar across the groups. Overall, dysplasia rates were the highest among the lesions located proximally to the transverse colon, which is consistent with other studies on smaller lesions [28]. In addition, although the large SSPs in the solitary SSP group were significantly smaller, their similar rate of dysplasia confirms previously published findings that size is not the only factor contributing to dysplasia, and that perhaps when they have reached a certain size, SSPs are at high risk of developing dysplasia [6]. An association has also been shown between increasing age (≥ 65 years) and dysplasia [6], which might somewhat confound the effect of size in this study and help to explain why the rates of dysplasia in this study are relatively high.

Substantial demographic similarities were detected between the three groups in terms of sex, age, and personal and family history of CRC. This suggests that a predilection to developing (large) SSPs is likely to be due to pathogenic mechanisms common to all three groups. However, the expressed colonic phenotype of solitary vs. multiple lesions may be related to an interaction with environmental factors, such as the colonic microenvironment [30], cigarette smoking, obesity, and alcohol intake [26, 31].

Finally, we found that SPS was recognized by the referring physician in only 9.0 % of cases. A study by Vemulapalli and Rex [32] described similar results, and this was thought to be due to insufficient application of the WHO criteria for SPS and a failure to detect serrated lesions during the first colonoscopy. We also found that failure of referrers to recognize SPS was mainly due to nondetection of synchronous lesions. This suggests that further education regarding techniques of endoscopic recognition of serrated polyps and SPS in the wider endoscopic community is warranted, but also that when a solitary large SSP is found, careful examination of the remaining colonic mucosa is of paramount importance, as in a subgroup of patients more lesions may be found. Implementation of the serrated polyp detection rate may be a helpful tool to increase detection rates [33].

The strengths of this study include the well characterized population, and the robust demographic and lesion data. There are some limitations. As all lesions were collected from a single tertiary center from patients referred for endoscopic removal of an SSP ≥ 20 mm, the study design includes inherent referral bias. Secondly, only the data pertaining to the index procedure

| Table 4 Summary of endoscopic and clinical differences and similarities between patients with serrated polyposis syndrome (SPS), a solitary large sessile serrated polyp (SSP), and oligo-SSP. Highlighted results indicate statistically significant differences compared with the SPS group. |

<table>
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<th></th>
<th>SPS</th>
<th>Solitary SSP</th>
<th>Oligo-SSP</th>
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<tr>
<td><strong>Endoscopic features</strong></td>
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<tr>
<td>Median size in mm</td>
<td>30</td>
<td>25</td>
<td>30</td>
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<tr>
<td>Submucosal fibrosis</td>
<td>+</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Hepatic flexure and proximal location</td>
<td>+</td>
<td>++</td>
<td>+</td>
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<td><strong>Clinical significance</strong></td>
<td></td>
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<tr>
<td>Patient demographics 2</td>
<td>=</td>
<td>=</td>
<td>=</td>
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<tr>
<td>Personal history of colorectal carcinoma</td>
<td>++</td>
<td>+</td>
<td></td>
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<tr>
<td>Family history of colorectal carcinoma</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Dysplasia within the SSP</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td><strong>Synchronous polyp burden</strong></td>
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<tr>
<td>≥ 1 advanced adenoma</td>
<td>++</td>
<td>+</td>
<td>++</td>
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<tr>
<td>≥ 10 conventional adenomas</td>
<td>++</td>
<td>–</td>
<td>+</td>
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</table>

SPS, serrated polyposis syndrome; SSP, sessile serrated polyp; –, feature is absent; + feature is present; ++, feature is numerically more frequent in this group than in the + group; =, feature is equal between the groups.

1 Patients with at least two SSPs (at least one of which was ≥ 20 mm) without fulfilling the criteria of SPS.

2 Patient demographics include sex and age distribution.
and first surveillance colonoscopy were collected prospectively. Data relating to the diagnostic procedure were collected retrospectively by systematic review of the patient chart. This may have resulted in an underestimation of polyp burden if, for example, all polyps removed at the diagnostic procedure were not noted in the report. However, including two further procedures with prospective data collection means a reasonable account of the patients’ true synchronous polyp burden over the study period is likely to have been observed. As the waiting period for EMR is 1–3 months and the first surveillance colonoscopy is performed within 4–6 months, all procedures were performed within 1 year, and this was therefore considered an acceptable time period from which to evaluate the prevalence of synchronous lesions within this cohort and to make the diagnosis of SPS. We acknowledge, however, that patients may develop more lesions over time and therefore fulfill the WHO criteria of SPS at a later stage. The time period over which the diagnosis of SPS should be made is currently unclear, though it is generally agreed that the qualifying serrated lesion count can be cumulative over several colonoscopies. An earlier diagnosis and hence early recognition of this high risk group is likely to lead to better clinical outcomes.

We excluded patients who underwent surgery (e.g. because of submucosal invasive cancer in the specimen) after the endoscopic resection procedure, as they did not have a comparable number of colonoscopic examinations during the study period and could not be compared with the rest of the population for synchronous polyp burden. We acknowledge that the exclusion of these patients with a potentially more aggressive phenotype may have resulted in attenuation of the end points observed in the study. We also acknowledge that in patients with a prior history of surgery (often for CRC), the polyp burden may have been altered, and that some of these patients may have met the diagnosis for SPS if referred for endoscopic assessment prior to surgery.

Family history for colorectal carcinoma and SPS was obtained from both patient charts and directly from the patient at the index procedure. Therefore, if the patient could not recall a history of CRC or SPS occurring in first-degree relatives this was noted as not present. This may have resulted in lower observed rates than the actual rates of personal and family history of colorectal cancer or SPS occurring in first-degree relatives this was noted as not present. This may have resulted in lower observed rates than the actual rates of personal and family history of CRC. Furthermore, the oligo-SSP group was relatively small, containing only 26 patients; therefore, the lack of any significant differences found between this and the SPS group may have resulted from a lack of power.

In conclusion, the group of patients with at least two SSPs, at least one of which was ≥20 mm, and without fulfilling the WHO criteria for SPS (oligo-SSP group), have similar rates of personal and family history of CRC and a similar synchronous polyp burden to patients with SPS. Therefore, appropriate counseling and scheduled surveillance, which may ideally be as frequent as patients with SPS, seems justified. Criteria for the diagnosis of SSPs may require revision to include the subgroup with oligo-SSP, as well as a temporal aspect to make application of this definition more practical; however, these results require independent validation. SSPs is infrequently recognized by endoscopists and therefore further training in detection of SSPs seems warranted. Although confirmatory data are necessary, solitary large SSPs may be able to return to standard surveillance following confirmation of complete endoscopic excision.

Competing interests

None

References


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