

The clinical impact of serrated colorectal polyps

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Abstract: Serrated polyps (SPs) of the colorectum pose a novel challenge to practicing gastroenterologists. Previously thought benign and unimportant, there is now compelling evidence that SPs are responsible for a significant percentage of incident colorectal cancer worldwide. In contrast to conventional adenomas, which tend to be slow growing and polypoid, SPs have unique features that undermine current screening and surveillance practices. For example, sessile serrated polyps (SSPs) are flat, predominately right-sided, and thought to have the potential for rapid growth. Moreover, SSPs are subject to wide variations in endoscopic detection and pathologic interpretation. Unfortunately, little is known about the natural history of SPs, and current guidelines are based largely on expert opinion. In this review, we outline the current taxonomy, epidemiology, and management of SPs with an emphasis on the clinical and public health impact of these lesions.

Keywords: serrated polyp, sessile serrated adenoma, sessile serrated polyp, traditional serrated adenoma, hyperplastic polyp, epidemiology, colonoscopy

Introduction

Colorectal cancer (CRC) remains the second leading cause of cancer-related mortality in the US despite widespread screening protocols.¹ Importantly, serrated polyps (SPs) have been identified as a unique pathway to CRC that may account for up to 35% of sporadically occurring CRCs.² These lesions have distinct molecular features that set them apart from the traditional “Fearon–Vogelstein” or “adenoma–carcinoma” model of tumorigenesis.³ In contrast to conventional adenomas, premalignant SPs are more prevalent in females, more frequently located in the proximal colon, and carry a novel genetic signature characterized by *BRAF* mutations, CpG island methylation, and microsatellite instability.⁴ Of particular concern, serrated pathway cancers represent a disproportionate number of interval CRC (i.e., cancers occurring after a negative screening test) and have appropriately become a target of public health investigation.⁵

The purpose of this review is to provide an overview of the taxonomy, epidemiology, and management of SPs.

Overview of SPs History

Much of the uncertainty surrounding SPs is driven by the fact that, historically, these polyps were all classified as hyperplastic polyps (HPs) and were considered innocuous, without malignant potential, and thus clinically unimportant. However, a series

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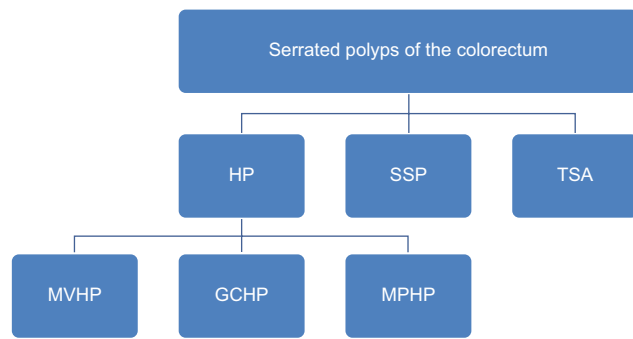


Figure 1 Serrated polyps of the colorectum.

Abbreviations: GCHP, goblet cell hyperplastic polyp; HP, hyperplastic polyp; MPHP, mucin-poor hyperplastic polyp; MVHP, microvesicular hyperplastic polyp; SSP, sessile serrated polyp; TSA, traditional serrated adenoma.

of case reports in the 1970s and 1980s began to question this long-held convention.^{6,7} The term “serrated adenoma” was officially coined in 1990 when Longacre and Fenoglio-Preiser used the name to characterize a series of premalignant lesions that had a “serrated glandular pattern simulating that seen in hyperplasia”.⁸ Further progress was made in 2008, when Torlakovic et al successfully differentiated sessile serrated polyps (SSPs) and traditional serrated adenomas (TSAs) on the basis of crypt architecture and molecular markers, setting the groundwork for modern classification systems.⁹ Currently, the World Health Organization (WHO) recognizes three major types of SPs: HPs, SSPs, and TSAs¹⁰ (Figure 1).

Taxonomy and histology

HPs

HPs are the most indolent of SPs and are characterized by straight crypts that rise perpendicularly from the muscularis

mucosae. HPs have a jagged infolding crypt epithelium that is more pronounced near the luminal surface, which gives them a “serrated” appearance¹¹ (Figure 2A). Endoscopically, these lesions are smooth, symmetric, pale, and tend to be distally located¹² (Figure 2B). HPs are subclassified histologically by the mucin content of their epithelial cells. Microvesicular hyperplastic polyps (MVHPs) exhibit cells with vacuolated cytoplasm containing numerous small mucin droplets. Goblet cell hyperplastic polyps (GCHPs) are composed almost entirely of goblet cells with large mucin-containing apical vesicles, and mucin-poor HPs have scant cytoplasmic mucin.¹³

SSPs

SSPs are distinguished from HPs by crypt distortion.^{9,14} In these lesions, the zone of proliferation migrates to the side of the crypt, causing disorganization and dilatation of crypt architecture.² Classically, these configurations are referred to as “boot” or “anchor-shaped” crypt bases^{2,15,16} (Figure 2C). On endoscopic examination, SSPs tend to be pale, larger than 5 mm, flat or only slightly raised, and smooth with irregular borders^{17–19} (Figure 2D). Many of these lesions excrete excessive quantities of mucin and are often covered with a thin, yellow, mucinous cap and/or surrounded by a “rim of debris”.¹⁹ Of note, there is some controversy about the terminology for these lesions, and other authors use different terms such as sessile serrated adenoma (SSA), SSA or SSP, or sessile serrated lesion (SSL). Herein, we use the term SSP to avoid confusion with conventional adenomas.

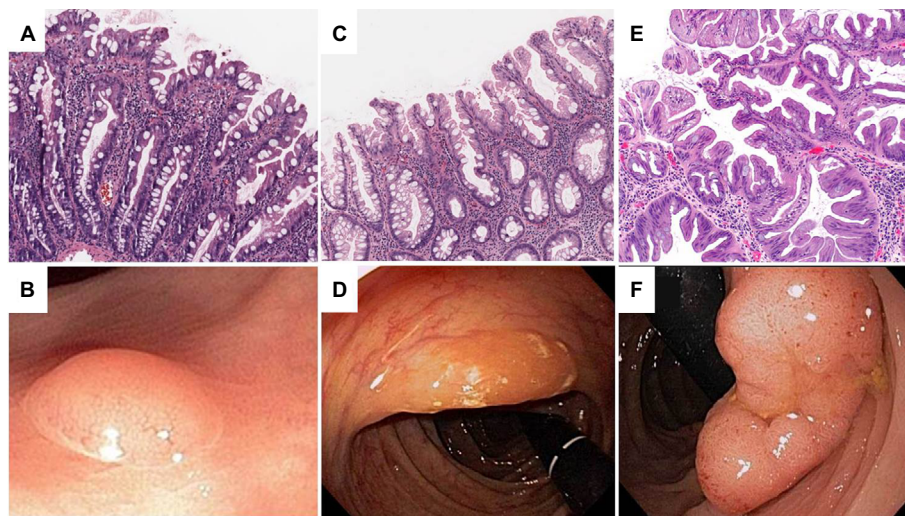


Figure 2 Endoscopic and histologic appearance of serrated polyps including (A, B) a microvesicular hyperplastic polyp, (C, D) sessile serrated polyp, and (E, F) traditional serrated adenoma.

Sessile serrated polyps with dysplasia (SSPDs) have similar crypt architecture and gross appearance to SSPs, but have dysplastic features including pseudostratification, hyperchromatic nuclei, and mitotic figures.²⁰ Approximately 15% of SSPs will have dysplastic features, and these lesions disproportionately affect women.¹⁵

TSA

Of all SPs, TSAs are the least prevalent, representing approximately 1% of SPs.¹⁵ Histologically, they represent a hybrid of serrated and conventional adenomas with “sawtooth” crypts haphazardly arranged in a tubulovillous pattern^{19,21} (Figure 2E). The defining feature of TSAs is ectopic crypt formation. Ectopic crypts lose their orientation to the muscularis mucosae and branch out at obtuse angles, creating villous projections into the lumen of the large intestine.^{2,21} A significant number of these lesions are frankly dysplastic and capable of malignant transformation, albeit through a different molecular pathway than SSPs.^{4,8,22} As TSAs are

typically more polypoid in form and located within the distal colorectum, they are more easily detected on endoscopy than SSPs^{23,24} (Figure 2F). All participants provided written informed consent for this study including publication of photography and image captured during colonoscopy.

The molecular pathways of serrated carcinogenesis

Conventional adenomas arise by the accumulation of a well-studied sequence of mutations involving *APC*, *KRAS*, and *p53*.²⁵ As the malignant potential of SPs has only recently been appreciated, the molecular underpinnings of serrated carcinogenesis are the subject of active research. From this, two primary pathways are emerging.

SSP pathway

A mutation in the *BRAF* oncogene is thought to be the inciting event of the SSP pathway⁴ (Figure 3). When present, *BRAF* mutations trigger downregulation of apoptosis and

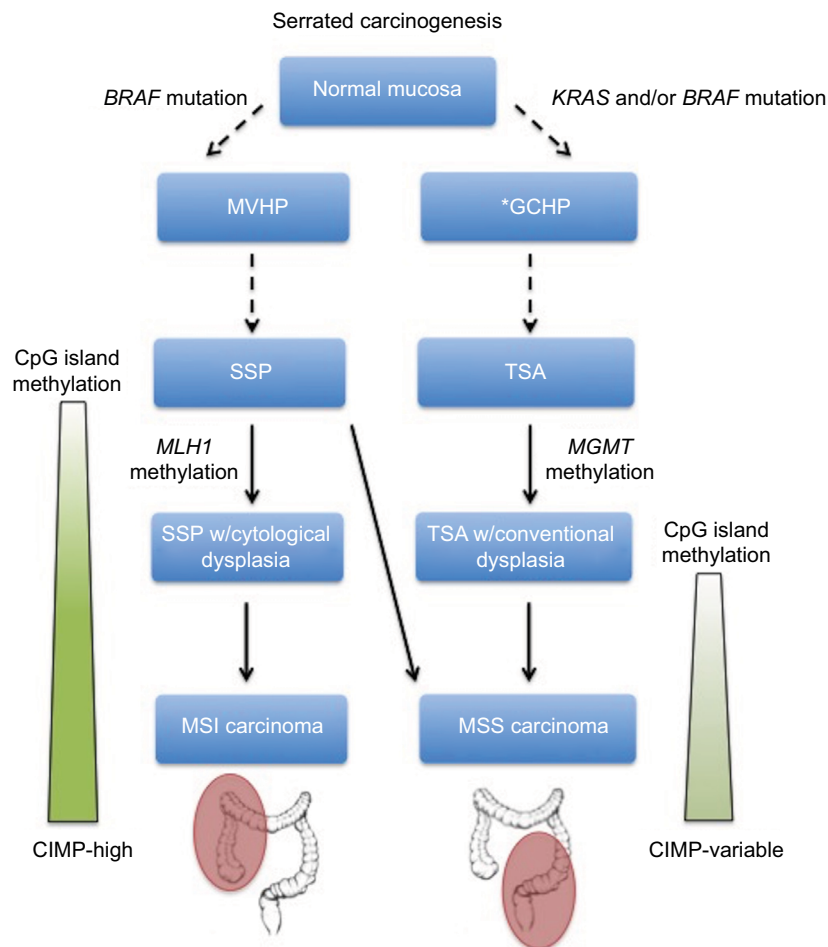


Figure 3 Serrated carcinogenesis.

Notes: *While GCHPs are theorized to be the precursor of TSAs, this link has not been definitively proven. Dashed arrows represent possible, but unproven steps.

Abbreviations: CIMP, CpG island methylation phenotype; GCHP, goblet cell hyperplastic polyp; MSI, microsatellite instable; MSS, microsatellite stable; MVHP, microvesicular hyperplastic polyp; SSP, sessile serrated polyp; TSA, traditional serrated adenoma.

promote cellular proliferation.²⁶ Secondly, hypermethylation of promoter regions causes epigenetic silencing of key regulatory genes.^{27,28} While some degree of methylation is present in nearly all types of cancer, serrated neoplasms in this pathway demonstrate global methylation of CpG islands and are thus classified as CpG island methylation phenotype-high (CIMP-H).²⁹ Epigenetic silencing of *MLH1*, a critical DNA mismatch repair gene, is thought to trigger the microsatellite instability (MSI) seen in serrated adenocarcinoma.^{30,31} As MVHPs have high rates of *BRAF* mutations, they are the favored precursors of SSPs.^{32,33} From this stage, increasing levels of epigenetic silencing facilitate progression to SSPD and, ultimately, MSI-High (MSI-H) CRC.^{4,34,35}

TSA pathway

The mechanism by which TSAs progress to CRC is less well understood, but has important differences with the SSP pathway (Figure 3). To begin with, TSAs are much more genetically diverse than SSPs. They may or may not have *BRAF* mutations and can be either CIMP-H or CIMP-low.²² Of importance, TSAs do have a high frequency of *KRAS* mutations, a key oncogene implicated in many types of malignancy, including the traditional adenoma–carcinoma sequence.^{22,36,37} Initially, activating *KRAS* and/or *BRAF* mutations causes uncontrolled cellular proliferation.^{4,38} Epigenetic silencing of the DNA repair gene *MGMT* then allows for the accumulation of subsequent mutations, ultimately leading to a subtype of CRC that is microsatellite stable.³⁹ As GCHPs have higher frequencies of *KRAS* mutations, they are hypothesized to be the precursors to TSAs, although no definitive link has been elucidated.³⁵ Given the genetic and phenotypic diversity of TSAs, it has been proposed that multiple distinct pathways exist.⁴⁰

Serrated polyposis syndrome (SPS)

SPS is a phenotypically diverse condition characterized by multiple concurrent SPs. The WHO defines SPS as: 1) at least five SPs proximal to the sigmoid colon, at least two of which are >10 mm in diameter; 2) any number of SPs occurring proximal to the sigmoid colon in an individual with a first-degree relative who has been diagnosed with SPS; or 3) >20 SPs of any size throughout the colon of a single individual.¹⁰ Based on a series of case studies, males and females appear to be equally affected and the mean age at presentation is in the sixth decade of life.⁴¹ While the true incidence of CRC in SPS is unknown, estimates from small case series are as high as 70%.^{42–44} Also, importantly, first-degree relatives of those who carry a diagnosis of SPS have an increased risk

of CRC.⁴⁵ There is growing evidence of a genetic etiology of SPS, but no proven hereditary basis, and routine genetic testing is not currently recommended.^{46–48} More research is needed to separate what is likely a number of molecularly distinct disease processes.

Epidemiology of SPs

Prevalence

Population-based studies estimate that roughly 40% of adults harbor at least one SP.^{17,33,49} Of these, HPs are by far the most common, representing 70%–90% of SPs.^{17,33,50} SSPs (10%–25%) and TSAs (~1%) make up a smaller proportion of SPs, respectively.^{15,17,33,51}

The prevalence of SSPs is estimated to be anywhere between 2% and 15% in average risk patients.^{15,17,52,53} However, the true prevalence may be even higher, as SPs are often subtle and likely underdetected on routine colonoscopy. The median age at presentation of SSPs is 61,¹⁵ and they are at least as common in females as males.^{15,33} In contrast to HPs, SSPs are predominately located on the right side of the colon.^{15,33,50}

Risk factors

Much of the epidemiologic data on serrated colorectal lesions predate the current classification system. However, important risk factors have emerged. Tobacco, alcohol, and obesity have consistently been identified as risk factors for SPs.^{54–60} These results were recently confirmed in a meta-analysis by Bailie et al, which reported increased risk for tobacco smoking (relative risk [RR], 2.47; 95% confidence interval [CI], 2.12–2.87), alcohol intake (RR, 1.33; 95% CI, 1.17–1.52), and body mass index (RR, 1.40; 95% CI, 1.22–1.61) when comparing the highest and lowest categories of exposure.⁶¹ While studies on protective factors are mixed,^{55,58,59} pooled data suggest that nonsteroidal anti-inflammatory drug use as well as diets high in folate, calcium, or fiber significantly reduce the risk of SPs.⁶¹ Interestingly, Caucasians appear to have a higher prevalence of SPs than do African-Americans or Hispanics.⁶²

With regard to SSPs, multiple studies have documented female sex as a significant risk factor^{15,33,51} (Table 1). Aggregate data on modifiable risk factors from Bailie et al suggest that smoking and alcohol are more strongly associated with SSPs than SPs as a whole.⁶¹ The role of obesity is less clear, and the available data are conflicting.^{59,61,63} A recent study by Davenport et al identified diets high in red meat and fat as important risk factors for SSPs, while simultaneously reporting that folate and fiber have a protective effect.⁶⁴

Table 1 Summary of literature on the risk factors for SSPs, including data from individual studies and meta-analysis where available

Risk factors	Studies, (n SSPs)	Results (OR/RR/IDR ^a [95% CI])
Age	Anderson et al, ⁶³ (n=90)	Per year increase: 1.05 (1.02–1.08)
	Buda et al, ⁵² (n=23)	<50 years: 1.00 (ref) 50–69 years: 5.8 (1.3–26.8) ≥70 years: 9.3 (1.9–45.4)
	Burnett-Hartman et al, ⁵⁹ (n=149)	<50 years: 1.00 (ref) 50–59 years: 1.63 (0.72–3.67) 60–69 years: 2.09 (0.87–5.00) ≥70 years: 2.19 (0.83–5.76)
Sex	Hetzel et al, ¹⁷ (n=46)	Per year increase: 1.00 (0.96–1.03)
	Burnett-Hartman et al, ⁵⁹ (n=149)	Male: 1.00 (ref) Female: 1.37 (0.82–2.28)
	Hetzel et al, ¹⁷ (n=46)	Female: 1.00 (ref) Male: 1.55 (0.93–2.61)
	Lash et al, ¹⁵ (n=2416)	Male: 1.00 (ref) Female: 1.21 (1.11–1.32)
Race	Burnett-Hartman et al, ⁵⁹ (n=149)	White: 1.00 (ref) African-American: 0.21 (0.02–2.14) Asian/Pacific Islander: 1.33 (0.54–2.44)
Socioeconomic status	Burnett-Hartman et al, ⁵⁹ (n=149)	High school or less: 1.0 (ref) Some college: 2.60 (1.08–6.24) College graduate: 3.35 (1.41–7.99) Graduate degree: 3.63 (1.55–8.54)
FH of CRC	Burnett-Hartman et al, ⁵⁹ (n=149)	No FH: 1.00 (ref) FH: 1.54 (0.97–2.43)
Smoking	Bailie et al, ⁶¹ meta-analysis	Never smoker: 1.00 (ref) Current/ever smoker: 3.40 (1.90–6.07)
Alcohol	Bailie et al, ⁶¹ meta-analysis	Low alcohol intake: 1.00 (ref) Higher/highest alcohol intake: 1.85 (1.03–3.32)
Obesity	Bailie et al, ⁶¹ meta-analysis	Low BMI: 1.00 (ref) BMI ≥ 30: 1.31 (0.89–1.92)
Physical activity	Bailie et al, ⁶¹ meta-analysis	Low physical activity: 1.00 (ref) High physical activity: 0.80 (0.43–1.48)
Diabetes	Anderson et al, ⁶³ (n=90)	Nondiabetic: 1.00 (ref) Diabetic: 4.57 (2.36–8.82)
Fiber intake	Davenport et al, ⁶⁴ (n=214)	Low fiber (<13 g/day): 1.00 (ref) High fiber (>25 g/day): 0.46 (0.19–0.68)
Dietary folate	Davenport et al, ⁶⁴ (n=214)	Low folate (<395 μg/day): 1.00 (ref) High folate (>812 μg/day): 0.51 (0.26–0.98)
Calcium intake	Davenport et al, ⁶⁴ (n=214)	Low calcium (<596 mg/day): 1.00 (ref) High calcium (>1217 mg/day): 0.54 (0.28–1.06)
Fat intake	Davenport et al, ⁶⁴ (n=214)	Low fat (<48 g/day): 1.00 (ref) High fat (>98 g/day): 3.09 (1.24–7.72)
Red meat intake	Davenport et al, ⁶⁴ (n=214)	Low red meat (<16 g/day): 1.00 (ref) High red meat (>73 g/day): 3.38 (1.90–6.00)
NSAIDs	Bailie et al, ⁶¹ meta-analysis	Low/no use: 1.00 (ref) Regular/current use: 0.62 (0.42–0.92)
HRT	Bailie et al, ⁶¹ meta-analysis	Nonuser: 1.00 (ref) User: 1.41 (0.82–2.41)

Notes: Bolded results indicate statistical significance, ^amultivariate OR reported when provided.

Abbreviations: BMI, body mass index; CI, confidence interval; Ref, reference; CRC, colorectal cancer; FH, family history; IDR, incidence density ratio; OR, odds ratio; RR, relative risk; SSPs, sessile serrated polyps; NSAIDs, nonsteroidal anti-inflammatory drugs; HRT, hormone replacement therapy.

Interestingly, Burnett-Hartman et al found an independent association between a higher level of education and SSPs, but whether this represents a true association or is confounded by other factors (e.g., differences in bowel preparation) has yet to

be resolved.⁵⁹ Given their relative scarcity, there is a paucity of data on TSAs and their risk factors are largely unknown.

When interpreting epidemiologic studies on SPs, it is important to remember that early investigations did not

differentiate between subtypes of SPs, and even more recently reported data are hindered by pathologic misclassification, particularly the distinction between large proximal HPs and SSPs.

Natural history

True HPs, especially those that are small and located in the distal colon and rectum, are thought to have little or no malignant potential.²⁰ However, MVHPs and GCHPs may serve as important intermediaries in serrated carcinogenesis, as previously discussed.

In contrast, there is substantial evidence that both SSPs and TSAs have malignant potential. Various studies have documented foci of high-grade dysplasia and/or invasive adenocarcinoma developing within these lesions.^{15,16,65} Moreover, there are multiple case reports of SSPs found adjacent to MSI-H colorectal tumors.^{66–68} Overall, the rate of high-grade dysplasia in SSPs ranges from 1% to 16%,^{24,69–73} and it is estimated that around 6% of SSPs will develop into MSI-H CRC.⁷⁴

Of great debate is the concept of dwell time or the rate at which SSPs progress to CRC. Multiple observational studies have shown higher rates of serrated cancers than SSPDs, suggesting a rapid transition phase or a relatively truncated dwell time.^{34,75,76} Also, there are a few case reports of SSPs left in situ transforming into invasive CRC in less than a year.^{77,78}

Alternatively, Lash et al reported that the median age of patients with SSPs, SSPDs, and SSPs with foci of adenocarcinoma was 61, 66, and 76 years, respectively.¹⁵ The authors concluded that these results imply a slow, stepwise progression along the pathway of serrated carcinogenesis over a period of 15+ years. In addition, a retrospective case series of MSI-H carcinoma diagnosed at the site of previous polypectomy reported a mean of 7.3 years between initial polypectomy and cancer resection.¹⁶

Importantly, these studies are limited by the fact that SSPs are notoriously difficult to detect on endoscopy, are often incompletely resected, and were historically thought benign and unimportant. The true behavior of SSPs in vivo is extremely challenging to study for ethical and logistical reasons. Nevertheless, optimal screening algorithms demand a better understanding of the natural history of SPs and SSPs, in particular.

The risk of synchronous and metachronous neoplasia

SPs increase the risk for both synchronous (concurrent) and metachronous (future or interval) neoplasia. In a

cross-sectional analysis involving nearly 5000 patients, Li et al found that the presence of large (>10 mm) SPs was a strong predictor of synchronous advanced colorectal neoplasia (odds ratio [OR], 3.24; 95% CI, 2.05–5.13).⁷⁹ These results were later reinforced by two large multicenter studies reporting similar risks of synchronous neoplasia associated with large SPs.^{80,81} With respect to metachronous lesions, Schreiner et al reported an elevated risk of future advanced neoplasia in patients with proximal SPs on baseline colonoscopy (OR, 3.14; 95% CI, 1.59–6.20).⁸⁰ As previously highlighted, many of these large and/or proximal SPs would now be classified as SSPs.

Using the current pathologic classification, Hazewinkel et al⁸² and Ng et al⁸³ found increased risk for synchronous advanced neoplasia in large and proximal HPs as well as SSPs. These results were confirmed by a large, population-based case-control study from Denmark, which highlighted the risk for metachronous CRC in patients with SSPs, particularly those located in the proximal colon (OR, 12.42; 95% CI, 4.88–31.58).⁸⁴ A recent article by Melson et al suggests that the risk of metachronous advanced neoplasia in low-risk SPs is comparable to that of high-risk tubular adenomas.⁸⁵ Moreover, small observational studies estimate the risk of metachronous CRC in patients harboring SSPs to be as high as 12.5%.^{86,87}

Rates of synchronous and metachronous SSPs also appear to be elevated,^{87,88} and the observation that metachronous SSPs may be limited to those with preexisting SPs suggests a “field effect” phenomenon even in patients who do not meet the formal criteria for SPS.⁸⁸ Meanwhile, for those who carry a diagnosis of SPS, the presence of SSPDs, advanced adenomas, or combined WHO phenotypes 1 and 3 appears to increase the risk for CRC.⁸⁹

Taken together, these studies suggest that the risk of advanced neoplasia increases as one moves from distal to proximal colon, from small to large polyp size, and from HP to more advanced serrated lesions such as SSPs and TSAs. Due to these complexities, many experts have advocated for surveillance intervals specific to SPs.

Detection of SPs

Endoscopic detection

Notably, there is significant variation in the endoscopic detection rates of SPs (0%–22%) even among experienced gastroenterologists,^{17,90,91} and those practicing today may miss more than half of the SPs.^{17,90} Adequate bowel preparation is associated with better detection of flat lesions, in general, and SSPs, in particular.^{92,93} This stands to reason, given their subtle endoscopic appearance and typical location in the right colon, which is more often affected by suboptimal bowel cleansing.

Wijkerslooth et al showed that SSP detection rates were also associated with withdrawal times.⁹¹ Kahi et al found that the detection rate of SPs is correlated to that of conventional adenomas.⁹⁰ However, despite this correlation, it should be noted that there are endoscopists with high adenoma detection rates and low SSP detection rates and vice versa; this implies that overlapping, but not interchangeable skills are needed to detect clinically important SPs. Fortunately, the detection rate of SPs appears to be increasing over time, as their clinical significance gains recognition by endoscopists and pathologists alike.¹⁷ An emphasis on tracking the adequacy of bowel preparation, cecal intubation rates, and polyp detection rates is helping to bridge disparities in practice.⁹⁴

Alternative methods for detection

Standard colonoscopy is superior to other readily available CRC screening modalities in detecting SPs, as the use of blood-based stool tests, flexible sigmoidoscopy, and computed tomography (CT) enterography have obvious limitations. To begin with, SSPs are less likely to undergo spontaneous hemorrhage^{14,95} and their relatively low profile decreases the probability of trauma-associated injury.⁹⁶ Visualization of SSPs on CT enterography is complicated by their sessile or flat morphology, and flexible sigmoidoscopy simply does not reach the right side of the colon where SSPs predominate. In support of this, Chang et al found that fecal immunochemical testing (a more specific test of fecal occult blood from colonic source) has poor sensitivity for detecting even large SSPs.⁹⁷ A recent randomized controlled trial (RCT) comparing standard colonoscopy to CT colonography reported a superior SSP detection rate (4.3% vs. 0.8%) in the standard colonoscopy arm,⁹⁸ and Kahi et al revealed that more than half of the proximal advanced SPs had no distal lesions, highlighting the limitations of flexible sigmoidoscopy in CRC surveillance.⁹⁹

Of interest, fecal DNA studies have shown promise as a novel tool for CRC screening.^{100,101} While these assays reliably detect CRC, their sensitivity for SSPs >10 mm is in the range of 42%–66%.^{100,102,103} Fecal DNA tests are limited by their lack of molecular markers specific to serrated neoplasms, poor specificity when compared to other noninvasive tests (i.e., fecal immunochemical testing), and the need for follow-up invasive testing for positive results. Notwithstanding, preliminary studies of *BRAF* stool assays have shown potential,¹⁰⁴ leaving the door open for the development of fecal DNA tests with higher sensitivity for precancerous SPs.

Highlighting concerning areas of mucosa with dye, a technique known as chromoendoscopy, has proven to be a

useful tool in the detection of SPs.^{19,33} Multiple studies have demonstrated that this technique can improve detection of both conventional adenomas and SPs.^{105–108} However, use of chromoendoscopy substantially lengthens procedure times, which is the major limitation of this technique and undermines its usefulness as a screening modality. In the largest RCT to date, Kahi et al reported a modest increase in the detection of flat and small adenomas in the chromoendoscopy arm. However, specific data on SSP detection were not reported, and the authors concluded that the additional yield was modest and did not justify the routine use of screening chromoendoscopy.¹⁰⁸

Devices that allow for real-time histologic assessment of colonic mucosa during colonoscopy have also shown promise in the detection of SPs. Narrow-band imaging (NBI) with and without magnification are the most popular of these, and both have been proven to reliably differentiate adenomas with malignant potential from benign hyperplastic lesions.^{109–111} Several groups have developed and validated standard criteria by which to identify SPs utilizing NBI.^{112,113} However, a recent meta-analysis did not find strong evidence for the benefit of image-enhanced colonoscopy for detection of SSPs, and thus, studies specifically designed to assess SSP detection rates are needed before these modalities can be widely accepted.¹¹⁴

More recently, a number of devices aimed at exposing additional colonic mucosa have been developed, such as wide-angled lenses and retrosopes (Figure 4). These devices are designed to broaden the operator's visual field and help image the backs of colonic folds. Panoramic or wide-angled colonoscopy devices employ multiple lenses to nearly double the standard visual field, and a recent RCT showed significant decreases in adenoma miss rates over standard colonoscopy.¹¹⁵ Retroscope devices provide a continuous retroflexed view of the colonic mucosa as the scope is withdrawn and may also improve detection of adenomas and SSPs.^{116,117}

Endoscopic removal

In the absence of formal guidelines, there are limited data available to aid practicing gastroenterologists. However, most experts recommend that all SPs with the exception of small (<5 mm) distal HPs be removed.^{4,11,14,20,34} Even then, many suggest that these diminutive, rectosigmoid HPs be sampled randomly for histologic evaluation.²⁰

SPs are notoriously challenging to resect, given their sessile morphology, indistinct borders, and predominance for the right colon, and the rates of incomplete resection are high. Pohl et al found that rates of incomplete resection were much higher for SSPs than for conventional adenomas (31.0% vs.

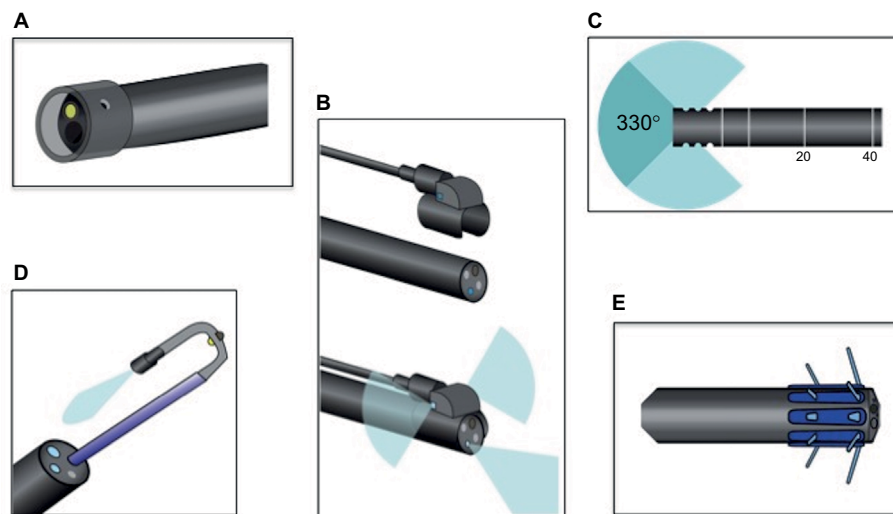


Figure 4 Novel colonoscopic technologies.

Notes: (A) Cap-assisted colonoscopy, (B) panoramic colonoscopy being attached to standard colonoscope and demonstrating added visual fields, (C) wide-angled colonoscopy demonstrating improved visual field with added lenses, (D) retro-scope colonoscopy through port of standard colonoscope, (E) endocuff colonoscopy.

7.2%) and that SSP histology was an independent risk factor for incomplete resection (RR, 3.74; 95% CI, 2.04–6.84).¹¹⁸ Of most concern, nearly half of large (>10 mm) SSPs were incompletely resected in this study, and there is evidence that incomplete polypectomy plays an important role in the development of interval CRCs.¹¹⁹

The optimal strategy for the resection of SPs depends on the location, size, and morphology of the lesion as well as the skill set of the individual endoscopist and the tools available with him or her. For smaller lesions, cold snare polypectomy has been found to be safe, while allowing for appropriate histologic evaluation of tissue margins.^{120,121} Larger lesions may require piecemeal resection with or without mucosal “lifting” with the injection of saline or another tissue expander to facilitate delineation and removal.^{122,123}

Pathologic interpretation

As the malignant potential of SPs is a relatively new concept, consistent pathologic interpretation remains a challenge.¹²⁴ Hetzel et al exposed significant variation in the classification of HPs and SSPs among practicing pathologists at a single academic medical center.¹⁷ In a large retrospective Canadian study, substantial numbers of proximal HPs (20%) and HPs >5 mm (17%) were reclassified as SSPs upon review by trained gastrointestinal pathologists, and these results were replicated in a recent European study.¹²⁵ Importantly, misclassification of SPs makes interpreting older studies of SPs (particularly those published prior to 2008) challenging, and even contemporary studies may include patients with older pathology readings that are not consistent with contemporary

criteria. While there is evidence that the pathologic diagnosis of SSPs is increasing with time,¹²⁶ educational outreach and seamless communication between gastroenterologists and pathologists are needed to improve diagnostic accuracy and ensure appropriate management.

Surveillance

Of critical importance to the management of SPs is the establishment of appropriate surveillance intervals. Both the US Multisociety Task Force and an international consensus panel have outlined a detailed strategy for the management of HPs, SSPs, SSPDs, and TSAs^{20,127} (Table 2). The latest European guidelines include no specific recommendations for SPs.¹²⁸ Of note, the consensus panel recommends more frequent surveillance in patients with proximal and/or large HPs, reflecting an appreciation of the aforementioned challenges in pathologic diagnosis. For patients diagnosed with SPS, annual colonoscopy is recommended.²⁰ An interval of 3–6 months is suggested for SPs requiring piecemeal resection or with positive margins on routine pathologic examination to ensure adequate resection.^{20,74,127}

Future directions

Improving our understanding of serrated carcinogenesis

The genetic and epigenetic drivers of the serrated pathway are incompletely understood. Identifying both the cause and the downstream effects of CpG island methylation may reveal additional tumor markers and/or novel therapeutic approaches. Also, a better understanding of the genetic basis

Table 2 Current recommendations for surveillance intervals after colonoscopy with serrated polyps

Histology	Size	Number	Location	Guideline-recommended surveillance interval (years)		
				Consensus ²⁰	US MSTF ¹²⁷	European ¹²⁸
HP	<10 mm	Any	Recto sigmoid	10	10	10
HP	≤5 mm	≤3	Proximal to sigmoid	10	No rec	No rec
HP	Any	≥4	Proximal to sigmoid	5	No rec	No rec
HP	>5 mm	≥1	Proximal to sigmoid	5	No rec	No rec
SSP	<10 mm	<3	Any	5	5	No rec
SSP	<10 mm	≥3	Any	3	5 ^a	No rec
SSP	≥10 mm	1	Any	3	3	No rec
SSP	≥10 mm	≥2	Any	1–3	3	No rec
SSPD	Any	Any	Any	1–3	3	No rec ^b
TSA	<10 mm	<3	Any	5	3	10
TSA	≥10 mm	1	Any	3	3	3
TSA	<10 mm	≥3	Any	3	3	1–3
Combined conventional and serrated polyps	Any	Any	Any	No rec	No rec	No rec
Serrated polyposis syndrome	See text	See text	See text	1	1	No rec

Notes: ^aNo specific recommendation regarding shortened interval for ≥3 SSPs. ^bEuropean guidelines recommend that “mixed polyps” be managed like conventional adenomas, which could include surveillance from 1 to 10 years based on the number and size of SSPDs.

Abbreviations: HP, hyperplastic polyp; US MSTF, US Multisociety Task Force; rec, recommendation; SSP, sessile serrated polyp; SSPD, sessile serrated polyp with dysplasia; TSA, traditional serrated adenoma.

of SPS would undoubtedly aid in the detection, classification, and management of these challenging cases. As our molecular diagnostics improve, we may come to recognize the separate phenotypes of SPS as distinct clinical entities.

Optimizing detection and resection

Perhaps the first obstacle to overcome with regard to improving the detection of SPs is the variation that currently exists between practicing endoscopists. Operators should strive to meet published standards for conventional adenomas. Based on available data, a detection rate of at least 1%–2% for SSPs is reasonable.¹²⁹ However, this likely underestimates the true prevalence of these lesions, as trials utilizing formal training programs and advanced endoscopic techniques report much higher numbers.^{33,130} Fecal DNA tests have shown promising results, but inclusion of serrated pathway markers is necessary to improve their ability to detect advanced precancerous lesions. Further advances in endoscopic imaging may lead to improvement in SSP detection, but this remains to be seen.

There is uncertainty with respect to the optimal methods to resect SPs. As previously mentioned, rates of incomplete resection are currently above acceptable thresholds.^{17,94} Clarification with regard to which lesions may benefit from submucosal lifting, chromoendoscopy, hot vs. cold snare technique, and/or underwater resection is necessary.^{131–133} Whether or not certain snare designs (e.g., crescent-shaped,

stiff, or braided wire snares) are superior to others for the resection of SSPs and other flat polyps is also an area where additional data are needed.

Clarifying surveillance intervals

Understanding the natural history of SPs is essential to outlining appropriate surveillance intervals. Current guidelines vary and are not based on robust data. Well-designed epidemiologic studies of MSI-H, proximal, and interval CRCs may provide useful information about the dwell time of SPs. In addition, the identification of molecular and histologic features associated with rapid progression would be invaluable.

As our power to detect even the subtlest colonic lesions increases, there are appropriate concerns about the added risk of consequent resections and surveillance. Especially in the arena of cancer screening, gastroenterologists must be careful not to upset the delicate balance between benefit and harm. Surveillance recommendations are fluid and likely to change as our understanding of serrated carcinogenesis improves, and this is a rapidly evolving field. Therefore, current practice must continually be reappraised to ensure the optimal care of patients harboring SPs.

Conclusion

Serrated neoplasms are responsible for a third of newly diagnosed CRC, a disproportionate number of which are interval cancers and occur despite recommended screening. Despite

progress, pathologic misclassification and endoscopic under-detection of SPs remain significant challenges. Innovations such as NBI, wide-angle colonoscopy, and fecal DNA testing are promising, but additional study is needed to ensure these technologies improve SP detection and decrease CRC incidence. Future investigations should focus on understanding the natural history of SPs, identifying risk factors for rapid progression and optimizing the detection and resection of these lesions.

Disclosure

The authors report no conflicts of interest in this work.

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