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Sessile Serrated Polyps: Detection, Eradication, and Prevention of the Evil Twin

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Opinion Statement

The sessile serrated polyp (SSP), also known as sessile serrated adenoma, is the evil twin among the colorectal cancer precursors. As will be described, these lesions have multiple aliases (serrated adenoma, serrated polyp or serrated lesion among others), they hang out in a bad neighborhood (the poorly prepped right colon), they hide behind a mask of mucus, they are difficult for witnesses (pathologists) to identify, they are difficult for police (endoscopists) to find, they are difficult to permanently remove from society (high incomplete resection rate), they can be impulsive (progress rapidly to CRC) and enforcers (gastroenterologists) don't know how best to control them (uncertain surveillance recommendations). There is no wonder that there is a need to understand these lesions well, learn how best to prevent the colonic mucosa from going down this errant path or, if that fails, to detect these deviants and eradicate them from colonic society. These lesions should be on the endoscopists' most wanted list.

Keywords

Serrated Polyp; Serrated Adenoma; Colonoscopic Detection; Polypectomy; Colon polyp Surveillance

Introduction

The goal of this review is to provide an update on the detection, eradication and prevention of SSPs. There are two closely related pathology issues that have had a major impact on approaches to understand the importance of these colorectal cancer precursors including the pathologic terminology and histo-molecular identification of the various types of serrated polyps.

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Conflict of Interest

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Terminology

Within the last 2 decades, our knowledge of colorectal SSPs has transformed dramatically and it has led to marked changes in the terminology used to describe the spectrum of serrated polyps. Prior to the 1990s, essentially all serrated polyps were called hyperplastic polyps (HP) and it was thought these lesions had no potential for malignancy. In the 1990s, Longacre and Fenoglio-Preiser et al coined the term “serrated adenoma” to describe a class of polyps that “exhibited the architectural but not the cytologic features of a hyperplastic polyp” [1]. The identification of this lesion, now called a traditional serrated adenoma (TSA), helped lead to a careful re-evaluation of the entire class of serrated colonic polyps by Torlakovic et al [2]. It is now believed that specific subsets of serrated polyps account for over 30% of colorectal cancers (CRCs) [3, 4].

Suffice it to say that the pathologic definitions and terminology used to describe what we now term SSPs has evolved substantially over the last 20 years; a sampling of terms that have been used include giant or large hyperplastic polyp, epithelial polyp, mixed hyperplastic/adenomatous polyp, serrated lesion, serrated polyp and serrated adenoma. Variability in both terminology and definitions has hindered our understanding of this field. In an attempt to standardize the terminology, the World Health Organization (WHO) updated their classification of serrated polyps in 2010 into 3 categories: 1) hyperplastic polyps 2) sessile serrated polyps (SSP) with or without cytologic dysplasia (CD) and 3) traditional serrated adenomas [5]. The WHO suggests the terms SSP and sessile serrated adenoma may be used interchangeably; we will use SSP in this review. It is believed that there is a “serrated” pathway to CRC that has a characteristic histologic and molecular progression from a subset of HPs to SSPs to SSPs with cytologic dysplasia (SSP-CD) to serrated CRCs (Figure 1) and that this pathway is more common in the proximal than distal colon [3]. Although TSAs are also thought to have malignant potential they are much less common than SSPs. This review will focus on the detection, eradication and prevention of SSPs.

Pathologic Identification

The recognition of SSPs as an important cancer precursor is now well established and there is a growing acceptance of the WHO classification of serrated polyps. It is generally agreed that SSPs have extension of serrations to lower levels of the crypt and extension of the proliferating cells to higher levels of the crypt rather than being limited to the upper crypt as seen in HPs. In addition, the crypt bases in SSPs can appear dilated and branched and may have a boot, “L”, or anchor shape (Figure 1); so called SSP-like crypts. Despite this general agreement there remains variability in the identification and classification of serrated polyps among pathologists. Some of the variability is based on differences of opinion regarding diagnostic criteria. For example, the WHO diagnosis of SSPs is based in part on the presence of 2 or more contiguous SSP-type crypts, whereas a recent review by an expert panel said that the presence of even one unequivocal architecturally distorted, dilated, and/or horizontally branched crypt is enough for an SSP diagnosis [3]. Use of the more lax criteria would be expected to increase the frequency of classifying polyps as SSPs. Indeed, Bettington et al reported a modest increase in SSP diagnosis using the more lax criteria (14.7% versus 12.1% with the WHO criteria) [6].

It has long been suspected that many polyps that had previously been classified as HPs were probably SSPs. Recent papers have helped quantify the magnitude of this misclassification. In 2010, Kim et al re-evaluated the pathology of 49 serrated polyps larger than 1 cm that had previously been reported as HPs and re-classified almost 20% as SSPs [7]. More recently, Tinmouth et al found that almost 30% of HPs larger than 5 mm removed between 2003 and 2008 were reclassified to SSPs upon review using current WHO criteria [8]. Similarly, Singh and colleagues reviewed over 4,000 pathology reports from 2009 by 25 different pathologists, of which 20% were initially characterized as serrated colon polyps. Seventeen percent of proximal HPs and 20% of serrated lesions over 5 mm were reclassified as SSPs [9]. Thus it likely that a significant number of SSPs are still misclassified in daily practice.

The high misclassification rate of proximal and large serrated polyps has led some experts to recommend that any serrated polyp (including hyperplastic polyps) larger than 1 cm in size be considered an SSP and this recommendation has directly impacted surveillance guidelines for serrated polyps as described below [3, 10]. Histologic misclassification has also confounded both clinical and molecular studies of serrated polyps. As a result, many retrospective studies that are not able to re-review the pathology have looked at proximal serrated polyps as a group as a surrogate for SSPs.

Molecular Identification

The serrated pathway to CRC appears to have characteristic molecular as well as histologic features (Figure 1). Whereas the conventional adenoma-carcinoma sequence involves the sequential acquisition of mutations (i.e. *APC/KRAS/P53*) that ultimately leads to chromosomal instability and tumor development [11], the serrated pathway appears to be driven by both genetic and epigenetic events [3, 11, 12]. Mutations in the *BRAF* gene and abnormal methylation of DNA termed the CpG island methylator phenotype (CIMP) are frequently found in HPs and SSPs and are thought to be early events in the serrated pathway. Later in the serrated pathway CIMP often leads to hypermethylation of the DNA mismatch repair gene *MLH1*, leading to its epigenetic silencing. This, in turn, causes defective mismatch repair and microsatellite instability (MSI). It is not clear how long it takes to progress through the early steps of the serrated pathway, although it has been estimated that it takes about 8 years on average to progress from an HP to an SSP but the later events are thought to occur more rapidly [13]. Loss of *MLH1* is typically seen in the dysplastic foci of SSP-CD and the resultant MSI is thought to lead to rapid progression to CRC in a manner analogous to the accelerated adenoma-carcinoma sequence known to occur in Lynch syndrome [3, 14]. SSP-CDs are thought to be the immediate precursors of sporadic MSI-H CRCs. Past studies of the molecular features of SSPs have been hindered by the histologic misclassification described above, but it is possible that molecular as well as pathologic criteria can be used together to more reliably identify these critical lesions.

Elucidation of the clinical and molecular features of SSPs and serrated adenocarcinomas (*BRAF* mutant, CIMP-H, MSI-H) have demonstrated that this pathway contributes disproportionately to the development of CRCs that occur in screened individuals before their next scheduled screening test; these CRCs have been called interval CRCs. Multiple studies have shown decreased benefit of screening colonoscopy for prevention of CRCs in

the proximal compared to the distal colon [15, 16]. These proximal interval CRCs tend to have CIMP and *BRAF* mutations more commonly than non-interval CRCs, suggesting that the serrated pathway is a preferential contributor to interval CRCs [17, 18]. This differential risk could be due to a more rapid progression of the serrated pathway to CRC, but it seems more likely that the failure to detect and/or completely remove SSPs are the major contributors. It has been estimated that 50% to 75% of interval CRCs are the result of missed or incompletely resected lesions, and that less than 30% are due to rapidly progressing lesions [19–21].

Detection

SSPs are difficult to detect. They are more common in the right colon where the prep is often poor, they tend to be flatter with paler mucosa than conventional adenomas, and they are often covered with a mucus cap. Given their endoscopic subtlety and their definite potential for transformation to malignancy, these lesions have proven to be a challenging dilemma to practicing gastroenterologists.

Prevalence of Serrated Polyps

Older studies have suggested that the prevalence of SSPs ranged from 0.6%–5.3%, however many of these investigations did not use the current WHO standard terminology for the histological classification of serrated polyps [5, 22–26]. The true prevalence of SSPs is dependent on both the detection rate and the correct pathologic classification of these lesions, and there is evidence of considerable variability of both these factors.

Kahi et al reported results of a retrospective review of 6,681 screening colonoscopies performed by 15 endoscopists at 2 U.S. academic endoscopy units. A total of 11,049 polyps were detected of which 51% were adenomas, 36% were serrated polyps and 11% (N=1238) were proximal serrated polyps. There was a significant ($p<0.0001$) variability in the rates of detection of any proximal serrated polyp with rates ranging from 1% to 18% which is substantially greater than the 2.8 fold range in variability of conventional adenoma detection rates (ADRs) among the same endoscopists [27]. De Wijkerslooth et al reported similar results in a prospective study of 1,354 patients undergoing screening colonoscopy at 2 academic centers in the Netherlands. A total of 1,635 polyps were detected of which 42% were serrated and 13% of those were proximal to the splenic flexure. The proximal serrated polyp detection rate differed significantly among endoscopists ranging from 6% to 22% [28].

The histologic classification of SSPs also varies significantly among pathology laboratories. For example, Payne and colleagues reviewed the range of reported prevalence of significant proximal serrated polyps found at screening colonoscopy in 7,215 patients at 32 endoscopy centers. Each center individually interpreted the pathology, with significant serrated lesions in the proximal colon defined as HPs greater than 10 mm, SSPs, and TSAs. The detection rate of significant proximal serrated lesions among the 32 centers varied greatly ranging from 0 to 9.8% and the authors noted that some pathologists never identified proximal serrated lesions as SSPs [29].

One recent study tried to control for both variability in detection and pathologic classification in order to estimate a more precise prevalence of SSPs. The authors reported the results of 1,910 screening colonoscopies in average-risk, asymptomatic patients performed by a single, high adenoma detecting endoscopist with histologic interpretation by a single, experienced GI pathologist. All serrated rectosigmoid polyps >5 mm and serrated polyps proximal to the sigmoid colon were included. One or more serrated polyps were found in 389 of 1,910 patients (20%). The prevalence of SSPs was 7.4% and that of SSP-CDs was 0.6% [30].

Both Kahi et al [27] and Payne et al [29] have reported that the proximal serrated polyp detection rate was significantly correlated with the adenoma detection rate (ADR) of an individual endoscopist. Some of the causes of the variability in SSP detection seem to be similar to those reported for the ADR variability. For example, longer withdrawal times, which are known to be associated with higher ADRs, have also been reported to be significantly associated with better proximal serrated polyp detection [28, 31]. In contrast, poor bowel prep is known to impair detection of conventional adenomas but, surprisingly, it hasn't been consistently shown to impair SSP detection [28, 32]. A recent cross sectional study, for example, compared the impact of optimal versus poor bowel preparation on polyp detection rates in a registry of over 13,000 patients using a standardized bowel preparation scale. The authors found that the proximal ADR rates were statistically lower in the poor preparation category than in adequately prepared colons, however the serrated polyp detection rate (SPDR), while numerically lower, was not statistically so (odds ratio 0.45, CI 0.24–0.84 and 0.75, CI 0.31–1.80 respectively) [32]. Similar results were reported in a prior study that reviewed 1,300 patients undergoing screening colonoscopy [28]. Postulated explanations for these unexpected results include residual stool being attached to mucous caps highlighting SSPs, additional washing of the colon leading to greater attention to the mucosa, or the fact that SSPs are less common than conventional adenomas and the studies were not adequately powered to show a difference in SPDR as a function of prep quality. Other factors such as patient age and sex have not been shown to significantly influence the SPDR.

Improving Detection of SSPs-Endoscopic morphology

Substantial recent efforts have been made to improve the overall endoscopic detection of SSPs and to define their specific features. In 2011, Tadepalli and colleagues retrospectively analyzed video clips of 158 SSPs detected during routine high-resolution colonoscopy. They characterized 7 morphologic descriptors of SSPs that were consistently found in SSPs. The most common features that first captured the endoscopists' attention to the lesion were termed "sentinel signs" and included a mucous cap (25%), alteration of the contour of a mucosal fold (25%), a rim of debris or bubbles (21.7%), and a dome-shaped protuberance (20.3%). Although not the initial sign, an interruption of the underlying mucosal vascular pattern was found in 32% of the SSPs. Over 90% of the SSPs were minimally elevated (less than 2.5 mm above the adjacent flat mucosa) and had Paris Classification Type 0–II morphology [33]. Another review by an expert panel identified similar sentinel signs, and described less common morphologic features such as a subtle nodularity seen in 9% of SSPs [3].

Chromoendoscopy (CE) and Image Enhanced Endoscopy

Chromoendoscopy (CE) and image enhanced endoscopy, particularly narrow band imaging (NBI) and autofluorescence imaging (AFI), are well established tools for distinguishing adenomas from hyperplastic polyps but less useful for improving ADRs [34]. A meta-analysis in 2012 found that compared to white light, NBI did not improve the ADRs [35]. In addition, a recent comprehensive meta-analysis of all of these techniques found that none of the image enhancing approaches improved ADRs except for CE [36].

SSPs also have characteristic CE and NBI features. Kashida et al reported that SSPs have a 'starlike' pit pattern with CE that distinguished them from TSAs and adenomas but was similar to the pattern in typical HPs [37]. Using NBI, the mucus caps over SSPs appears red, the underlying mucosa can appear almost white, and large dark spots may be seen inside the crypts. NBI imaging has been used to distinguish serrated polyps from adenomas and NBI characteristics of SSPs have also been described in this context. In a recent study, a cloud-like, bumpy, soft-looking nodular surface with indistinct borders, irregular shape and dark spots inside the crypts were found to be endoscopic predictors of SSP histology. If all of these features were present (compared to none), they showed high sensitivity (89%), specificity (96%), and accuracy (93%) for predicting SSP histology [38].

It is not known if the use of either CE or image enhanced endoscopy can increase the detection rate of sporadic SSPs but NBI has been reported to increase polyp detection rates in patients with serrated polyposis syndrome (SPS). Boparai et al compared the miss rate of serrated polyps in patients with SPS using high resolution endoscopy (HRE) followed by NBI and vice versa. The overall polyp miss rate was 36% for HRE and 10% for NBI (OR 0.21; 0.09–0.45) [39]. Based, in part on this study, the European Society of Gastrointestinal Endoscopy recommends routine use of pan-colonic NBI, or CE, in patients with known or suspected serrated polyposis syndrome [40].

Other Detection Modalities

Proximal Retroflexion—Retroflexion of the colonoscope in the proximal colon has been performed in hopes of improving detection of inconspicuous polyps in this region. A small RCT and an observational descriptive cohort study have suggested that proximal retroflexion is no better in detecting additional polyps compared to a forward view "second look" of the proximal colon during routine colonoscopy. However proximal retroflexion appears to be easily performed with minimal risk, and may have a role in assessing and removing larger flat polyps [43].

Water Immersion—Recently, a retrospective consecutive group observational study compared water-immersion with cap-assisted colonoscopy (WCC) to white light colonoscopy, and found that WCC was associated with a higher ADR (75.0% vs. 59.4%; $P = .02$), proximal colon ADR (61.0% vs. 47.5%; $P = .07$) and proximal colon serrated polyp detection rate (24.0% vs. 9.9%; $P = .009$) [44]. This result awaits confirmation.

Endocystoscopy—A newer technology, known as endocystoscopy, has the potential to better delineate colonic lesion characteristics. Endocystoscopy is an ultra-high magnification

technique that enables surface morphology to be assessed in real time, with magnifications in excess of 450×. This technology requires staining of the mucosa with crystal violet or methylene blue, and uses a high-power fixed-focus objective lens that can either be incorporated into the endoscope or comes in a probe-based system [45]. Using this technology, stellar & papillary pit patterns with open pits (Kudo Type II-O) have been found to be highly specific (97%) for SSPs with a sensitivity of 66% [46, 47]. Kutsukawa and colleagues reported similar results in a retrospective review of endoscopic features of 58 pathologically diagnosed serrated polyps. Lumen and nuclei patterns were recorded and what was noted was Kudo Type II patterns were significantly characteristic of hyperplastic polyps, while oval lumens (Kudo Type II-O) were significantly characteristic of SSPs [48]. While intriguing, endocytoscopy is currently a research tool and is unavailable in many western countries. Even if this technology is shown to improve the differentiation of SSP from other types of polyps, it is uncertain if it would be useful in increasing SSP detection rates.

Eradication

As noted earlier, SSPs contribute disproportionately to interval CRCs, and incomplete resection of colonic polyps in general on prior colonoscopy could account for 20–30% of interval cancers [20, 21, 49, 50]. Incomplete polyp resection occurs more commonly for SSPs than other types of colonic polyps. In the 2013 CARE study, Pohl and colleagues studied 269 patients who had a total of 346 resected non-pedunculated neoplastic polyps that ranged from 5–20 mm in size [19]. After the endoscopist thought the polyp had been completely eradicated, cold biopsies were obtained from the resection margin to determine if the resection was complete. Of the resected polyps, 59.3% were right-sided and 10% were SSPs. Overall 10% of the polyps were incompletely resected and SSPs were more likely to be incompletely resected than adenomas (31% vs. 7%; RR 3.7). Strikingly, 48% of SSPs greater than 10 mm were incompletely resected. The incomplete resection rate ranged from 6.5% to 22.7% among 5 endoscopists [19]. Thus, in addition to a high ADR, skilled endoscopic technique to ensure complete polyp eradication is necessary to confer the ultimate benefit of polypectomy and this is particularly important for SSPs.

Polypectomy Techniques

All but the tiniest rectosigmoid, hyperplastic-appearing polyps should be completely endoscopically removed whenever feasible. As SSPs tend to be flat, large, and located in the proximal colon, concern may be raised over the safety of their removal. Currently the evidence suggests that removal of SSPs can be performed safely and does not lead to a higher rate of perforation than adenomas with similar characteristics [51, 52]. It has been recommended that all sessile polyps larger than 3 mm be removed with a cold or hot snare with a rim of normal surrounding tissue rather than with biopsy forceps to allow complete removal [3]. The edges of SSPs are often indistinct and narrow band imaging or chromoendoscopy can assist in ensuring their perimeter for complete removal. Submucosal injection of larger SSPs with a dye-containing liquid (i.e. methylene blue) can provide elevation of the lesion and nicely define polyp edges to improve the chance of obtaining adequate margins. The edges of the polypectomy site should be carefully assessed and any

residual polyp tissue should be completely removed; argon plasma coagulation or cautery with the snare tip are particularly useful for this purpose. If an SSP does not lift when performing injection techniques, it may be due to scarring from previous attempts at resection, or it may be an indication of invasive cancer and sampling may be prudent [53]. The decision of whether to undertake endoscopic resection of SSPs will ultimately depend on the lesion's characteristics and the endoscopist's skill level, but almost all lesions can safely be removed endoscopically with surgical resection rarely being required.

In situations where submucosal injection is not feasible, underwater EMR (UEMR) without injection, in the hands of experts, has been proposed as an alternative approach. One variant of this technique involves cap-assisted endoscopy with full water immersion for the entire procedure and piecemeal resection with a hot 15 mm "duck bill" snare. A pilot study of this technique reported the resection of 62 large (mean size 3.5 cm) sessile polyps (18% were serrated adenomas) in 60 patients. At a mean follow up of 20 weeks, none of 54 patients had evidence of incomplete resection [54]. Wang et al recently reported similar UEMR results with complete resection of 42 of the 43 lesions in a consecutive patient population referred for resection of large colorectal neoplasms (7% SSPs) [55].

Prevention

The usual approach to primary prevention of CRC or neoplastic colorectal polyps is to alter modifiable risk factors as well as utilize effective nutritional or chemopreventive agents. While tobacco use is associated with the presence of SSPs, there is relatively little else known about the primary prevention of SSPs. The focus of secondary prevention is on high quality surveillance colonoscopy, complete eradication of SSPs as described above, and finally on improving our recognition and understanding of SPS.

Risk Factors

For adenomas and CRC, many non-modifiable risk factors have been identified including increasing age, male gender, African American race, country of origin, a history of inflammatory bowel disease and a personal or family history of colonic neoplasia. In addition, modifiable risk factors for these lesions include obesity, lack of physical activity, alcohol and/or tobacco use and diets high in red meat and low in high-fiber foods [56–59]. Distal serrated polyps (mostly HPs) are also associated with tobacco use, lack of physical activity and low folate intake [60–63]. Unlike adenomas, however, SSPs have not been associated with increasing age or male gender and other risk factors such as obesity, family history of CRC or intake of alcohol, fiber, or calcium have not consistently been associated with either HPs or SSPs [61, 64, 65]. Even the association of SSPs with tobacco use is not totally consistent. Wallace et al found an association with tobacco use for left-sided advanced serrated polyps (including SSPs) but not for those in the right side [64]. However, smoking has been strongly associated with MSI-H CRCs [66] which arise from SSPs.

Chemoprevention

Aspirin Use

A systematic review by Algra found that regular aspirin use was associated with about a 20%–40% reduction in the risk of both CRC and colonic adenomas [67]. Wallace et al also reported that aspirin was associated with a reduced risk of both left and right-sided serrated polyps (RR 0.56 95% CI 0.34–0.91) [64]. Aspirin appears to prevent MSI-H CRCs in Lynch syndrome, but there is relatively little data about its effect on sporadic serrated CRCs [68]. In an older study, Chia et al found that long term NSAID users were less likely to develop microsatellite stable CRCs (OR 0.6; 95% CI 0.4–0.8) whereas there was no similar relationship with MSI-H CRCs (OR 0.9; 95% CI 0.5–1.4) [66].

The chemopreventive action of aspirin is thought to stem from its inhibition of COX-2 and subsequent decreased prostaglandin production. COX-2 has been found to be up-regulated in CRCs but Kawasaki et al reported that SSPs rarely show overexpression of COX2, thus, disputing a biologic rationale for NSAID chemoprevention for these polyps [69]. Similarly, Nishihara reported that regular aspirin use was not associated with a decreased risk of *BRAF* mutated CRCs (recall that *BRAF* mutations are a marker of the serrated pathway) [70]. *PIK3* mutation has been identified as a possible marker for the positive response to regular aspirin use as adjuvant therapy for CRC [71]. *PIK3* mutations are found in 10–20% of CRC but have been associated mainly with *KRAS* mutations and less consistently with markers of the serrated pathway such as CIMP, MSI, and *BRAF* mutations [72, 73]. Taken together, these data suggest that aspirin will not be effective in preventing CRCs derived from the serrated pathway.

Although the study by Wallace et al highlights the association between regular aspirin use and reduced risk of right-sided serrated polyps, the magnitude of the chemopreventive effect of aspirin is unknown and the data for serrated CRC prevention is weak [64]. Therefore, the regular use of aspirin for primary prevention of SSPs cannot currently be recommended.

Given the difficulty identifying patients at increased risk of SSPs, a risk score for identifying high-risk SSPs was developed by Bouwens et al using the predictive factors of age >50, history of SSP, tobacco use, and lack of aspirin use [74]. This score has not been studied well enough to recommend its use, but it can serve as a reminder to endoscopists about the relevant risk factors for SSPs.

Secondary Prevention

Current Guidelines for Surveillance

The natural history of serrated polyps is not well understood and controlled trials of screening and surveillance have not been done. As a result, surveillance guidelines are largely based on observational studies and expert opinion [3, 10, 75]. The US Multi-Society Task Force on Colorectal Cancer (MSTF) guidelines (Table 1) recommend a screening interval of 10 years for patients with only diminutive (<5mm) distal HPs. Surveillance intervals for patients with SSPs are based upon polyp characteristics including size, number and histology in a manner analogous to that for adenomas (colonoscopy surveillance at 5

years for 1–2 small SSPs and 3 years any large SSP) and treating SSPs-CD like advanced adenomas (colonoscopic surveillance in 3 years or less).

Guidelines from the National Comprehensive Cancer Network (NCCN) and those proposed by Rex et al are broadly similar to those in Table 1 [3, 75]. But, Rex et al provide more detailed surveillance recommendations including surveillance colonoscopy at 10 years for patients with 1–3 diminutive (<5 mm) proximal HPs, 5 years for any non-diminutive proximal HP or 4 diminutive proximal HPs and 1–3 years for 2 or more large (≥1 cm) SSPs in any location as well as for any SSP-CD [3]. These authors also emphasize the point that high quality colonoscopy is central to any surveillance program. Both the MSTF guidelines and those proposed by Rex et al recommend that large HPs be considered the same as SSPs [3, 10]. The definitive follow-up for SSPs should also reflect the completeness of the polyp removal. If a large SSP is taken out piecemeal, a repeat exam in 3–6 months is appropriate given the risk for incomplete resection [3, 75].

Although SSPs and conventional adenomas have distinct molecular pathways, the presence of both types of polyps in one patient appears to identify a higher risk population. In a retrospective cross-sectional study, for example, Vu et al. showed that patients with both types of lesions, tended to have large SSPs as well as more numerous and more advanced adenomas than patients with either type of polyp alone. Thus it seems reasonable to combine SSPs with adenomas when making surveillance recommendation (i.e. 1 SSP and 2 small tubular adenomas would warrant a 3 year follow up) [76].

Serrated Polyposis Syndrome (SPS)

SPS is characterized by the presence of multiple serrated polyps (SSPs, HPs, TSAs) throughout the colon. It is not yet known if SPS is hereditary. There is no mutation known to cause SPS and therefore the diagnosis is based on clinical criteria. The WHO criteria for SPS include a cumulative lifetime total of: 1) ≥5 serrated polyps proximal to sigmoid colon with ≥2 polyps >1 cm or 2) ≥20 serrated polyps of any size distributed throughout the colon (not limited to the rectosigmoid) or 3) ≥1 serrated polyp proximal to the sigmoid colon in a patient with a first degree relative of SPS [77]. The prevalence of SPS is unclear with estimates ranging from 1/100,000 to as high as 1/3,000; undoubtedly SPS is seriously under-diagnosed and the prevalence could be even higher than these estimates [78].

The risk of CRC in SPS is not well defined; case series have reported risks as high as 30–50%, and Boparai reported a CRC incidence of 7% at 5 years in patients undergoing regular surveillance [79–81]. It is recommended that all polyps >5 mm in size be removed in patients with SPS. Once the polyps are removed, surveillance every 1–3 years is recommended (Table 2) [3, 10, 75]. First-degree relatives of SPS patients have also been reported to have an elevated risk of CRC (5.4; 95% CI 3.7–7.8) and they are advised to undergo colonoscopy at age 40 or 10 years prior to CRC or SPS development in the affected relative, whichever is earlier (Table 2) [82].

Summary/Concluding Remarks

The SSP is a specific type (the evil twin) of colonic polyp that is central to the serrated pathway to CRC. Our understanding of this pathway continues to evolve rapidly, but it has already transformed thinking of colorectal carcinogenesis from the adenoma-carcinoma sequence to include the serrated polyp-carcinoma pathway with the SSP as the precursor of up to 30% of all CRCs. Molecular and genetic similarities link SSPs to MSI-H sporadic CRCs, and this knowledge was a critical component of the recognition of the serrated cancer pathway, clearly exemplifying the important contribution of molecular pathology to clinical care. It is now recognized that there are important issues that need to be addressed in this field including residual variability in pathologic terminology for the classes of serrated polyps, the high inter-observer variation in the pathologic identification of SSP, the high endoscopic miss rate and incomplete resection rate of SSP, and the under-diagnosis of SPS among others. Recognition of these problems has been the first step in developing solutions including increased pathologist awareness regarding the importance of these polyps, ensuring adequate proximal colon cleansing with split bowel preparations, and endoscopic techniques to improve visualization and lesion resection. High quality colonoscopy and complete polypectomy are the most effective way to prevent CRCs arising from the serrated pathway, and guidelines have now been developed that aids in the management of patients with serrated polyps. There is certainly more knowledge to gain in this area, but progress is clearly being made.

References

1. Longacre TA, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. *Am J Surg Pathol.* 1990; 14(6):524–37. [PubMed: 2186644]
2. Torlakovic E, et al. Morphologic reappraisal of serrated colorectal polyps. *Am J Surg Pathol.* 2003; 27(1):65–81. [PubMed: 12502929]
3. Rex DK, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol.* 2012; 107(9):1315–29. quiz 1314, 1330. [PubMed: 22710576]
4. Montgomery E. Serrated colorectal polyps: emerging evidence suggests the need for a reappraisal. *Adv Anat Pathol.* 2004; 11(3):143–9. [PubMed: 15096728]
5. Bosman, FT. World Health Organization., and International Agency for Research on Cancer. World Health Organization classification of tumours. 4. Lyon: IARC Press; 2010. WHO classification of tumours of the digestive system; p. 417
6. Bettington M, et al. Critical appraisal of the diagnosis of the sessile serrated adenoma. *Am J Surg Pathol.* 2014; 38(2):158–66. [PubMed: 24418851]
7. Kim SW, et al. A significant number of sessile serrated adenomas might not be accurately diagnosed in daily practice. *Gut Liver.* 2010; 4(4):498–502. [PubMed: 21253298]
8. Tinmouth J, et al. Sessile Serrated Polyps at Screening Colonoscopy: Have They Been Under Diagnosed? *Am J Gastroenterol.* 2014
9. Singh H, et al. Pathological reassessment of hyperplastic colon polyps in a city-wide pathology practice: implications for polyp surveillance recommendations. *Gastrointest Endosc.* 2012; 76(5): 1003–8. [PubMed: 23078924]
10. Lieberman DA, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology.* 2012; 143(3):844–57. [PubMed: 22763141]
11. Vogelstein B, et al. Genetic alterations during colorectal-tumor development. *N Engl J Med.* 1988; 319(9):525–32. [PubMed: 2841597]

12. Bettington M, et al. The serrated pathway to colorectal carcinoma: current concepts and challenges. *Histopathology*. 2013; 62(3):367–86. [PubMed: 23339363]
13. Yang S, et al. BRAF and KRAS Mutations in hyperplastic polyps and serrated adenomas of the colorectum: relationship to histology and CpG island methylation status. *Am J Surg Pathol*. 2004; 28(11):1452–9. [PubMed: 15489648]
14. Crockett SD, et al. Sessile Serrated Adenomas: An Evidence-Based Guide to Management. *Clin Gastroenterol Hepatol*. 2013
15. Singh H, et al. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology*. 2010; 139(4):1128–37. [PubMed: 20600026]
16. Brenner H, et al. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Ann Intern Med*. 2011; 154(1):22–30. [PubMed: 21200035]
17. Farrar WD, et al. Colorectal cancers found after a complete colonoscopy. *Clin Gastroenterol Hepatol*. 2006; 4(10):1259–64. [PubMed: 16996804]
18. Arain MA, et al. CIMP status of interval colon cancers: another piece to the puzzle. *Am J Gastroenterol*. 2010; 105(5):1189–95. [PubMed: 20010923]
19. Pohl H, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. *Gastroenterology*. 2013; 144(1):74–80.e1. [PubMed: 23022496]
20. Leung K, et al. Ongoing colorectal cancer risk despite surveillance colonoscopy: the Polyp Prevention Trial Continued Follow-up Study. *Gastrointest Endosc*. 2010; 71(1):111–7. [PubMed: 19647250]
21. Robertson DJ, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. *Gut*. 2014; 63(6):949–56. [PubMed: 23793224]
22. Sanaka MR, et al. Adenoma and sessile serrated polyp detection rates: variation by patient sex and colonic segment but not specialty of the endoscopist. *Dis Colon Rectum*. 2014; 57(9):1113–9. [PubMed: 25101608]
23. Hetzel JT, et al. Variation in the detection of serrated polyps in an average risk colorectal cancer screening cohort. *Am J Gastroenterol*. 2010; 105(12):2656–64. [PubMed: 20717107]
24. Kim HY, et al. Age-specific prevalence of serrated lesions and their subtypes by screening colonoscopy: a retrospective study. *BMC Gastroenterol*. 2014; 14:82. [PubMed: 24775268]
25. Hazewinkel Y, et al. Prevalence of serrated polyps and association with synchronous advanced neoplasia in screening colonoscopy. *Endoscopy*. 2014; 46(3):219–24. [PubMed: 24254386]
26. Lash RH, Genta RM, Schuler CM. Sessile serrated adenomas: prevalence of dysplasia and carcinoma in 2139 patients. *J Clin Pathol*. 2010; 63(8):681–6. [PubMed: 20547691]
27. Kahi CJ, et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. *Clin Gastroenterol Hepatol*. 2011; 9(1):42–6. [PubMed: 20888435]
28. de Wijkerslooth TR, et al. Differences in proximal serrated polyp detection among endoscopists are associated with variability in withdrawal time. *Gastrointest Endosc*. 2013; 77(4):617–23. [PubMed: 23321338]
29. Payne SR, et al. Endoscopic detection of proximal serrated lesions and pathologic identification of sessile serrated adenomas/polyps vary on the basis of center. *Clin Gastroenterol Hepatol*. 2014; 12(7):1119–26. [PubMed: 24333512]
30. Abdeljawad K, et al. Sessile serrated polyp prevalence determined by a colonoscopist with a high lesion detection rate and an experienced pathologist. *Gastrointest Endosc*. 2014
31. Butterly L, et al. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire Colonoscopy Registry. *Am J Gastroenterol*. 2014; 109(3):417–26. [PubMed: 24394752]
32. Anderson JC, et al. Impact of fair bowel preparation quality on adenoma and serrated polyp detection: data from the New Hampshire Colonoscopy Registry by using a standardized preparation-quality rating. *Gastrointest Endosc*. 2014; 80(3):463–70. [PubMed: 24818550]
33. Tadepalli US, et al. A morphologic analysis of sessile serrated polyps observed during routine colonoscopy (with video). *Gastrointest Endosc*. 2011; 74(6):1360–8. [PubMed: 22018553]

34. Sato R, et al. The diagnostic accuracy of high-resolution endoscopy, autofluorescence imaging and narrow-band imaging for differentially diagnosing colon adenoma. *Endoscopy*. 2011; 43(10):862–8. [PubMed: 21732270]
35. Pasha SF, et al. Comparison of the yield and miss rate of narrow band imaging and white light endoscopy in patients undergoing screening or surveillance colonoscopy: a meta-analysis. *Am J Gastroenterol*. 2012; 107(3):363–70. quiz 371. [PubMed: 22186978]
36. Omata F, et al. Image-enhanced, chromo, and cap-assisted colonoscopy for improving adenoma/neoplasia detection rate: a systematic review and meta-analysis. *Scand J Gastroenterol*. 2014; 49(2):222–37. [PubMed: 24328858]
37. Kashida H, et al. Endoscopic characteristics of colorectal serrated lesions. *Hepatogastroenterology*. 2011; 58(109):1163–7. [PubMed: 21937375]
38. Hazewinkel Y, et al. Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white-light endoscopy and narrow-band imaging. *Gastrointest Endosc*. 2013; 77(6):916–24. [PubMed: 23433877]
39. Boparai KS, et al. Increased polyp detection using narrow band imaging compared with high resolution endoscopy in patients with hyperplastic polyposis syndrome. *Endoscopy*. 2011; 43(8): 676–82. [PubMed: 21811939]
40. Kami ski MF, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2014; 46(5):435–49. [PubMed: 24639382]
41. Harrison M, Singh N, Rex DK. Impact of proximal colon retroflexion on adenoma miss rates. *Am J Gastroenterol*. 2004; 99(3):519–22. [PubMed: 15056095]
42. Hewett DG, Rex DK. Miss rate of right-sided colon examination during colonoscopy defined by retroflexion: an observational study. *Gastrointest Endosc*. 2011; 74(2):246–52. [PubMed: 21679946]
43. Pishvaian AC, Al-Kawas FH. Retroflexion in the colon: a useful and safe technique in the evaluation and resection of sessile polyps during colonoscopy. *Am J Gastroenterol*. 2006; 101(7): 1479–83. [PubMed: 16863549]
44. Yen AW, Leung JW, Leung FW. A new method for screening and surveillance colonoscopy: Combined water-exchange and cap-assisted colonoscopy. *J Interv Gastroenterol*. 2012; 2(3):114–119. [PubMed: 23805389]
45. Singh R, et al. Real-time histology with the endocytoscope. *World J Gastroenterol*. 2010; 16(40): 5016–9. [PubMed: 20976836]
46. Kudo S, et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc*. 1996; 44(1):8–14. [PubMed: 8836710]
47. Kimura T, et al. A novel pit pattern identifies the precursor of colorectal cancer derived from sessile serrated adenoma. *Am J Gastroenterol*. 2012; 107(3):460–9. [PubMed: 22233696]
48. Kutsukawa M, et al. Efficiency of endocytoscopy in differentiating types of serrated polyps. *Gastrointest Endosc*. 2014; 79(4):648–56. [PubMed: 24119508]
49. Patel SG, Ahnen DJ. Prevention of interval colorectal cancers: what every clinician needs to know. *Clin Gastroenterol Hepatol*. 2014; 12(1):7–15. [PubMed: 23639602]
50. Pohl H, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. *Clin Gastroenterol Hepatol*. 2010; 8(10):858–64. [PubMed: 20655393]
51. Gurudu SR, et al. Sessile serrated adenomas: demographic, endoscopic and pathological characteristics. *World J Gastroenterol*. 2010; 16(27):3402–5. [PubMed: 20632442]
52. Fahrtash-Bahin F, et al. Snare tip soft coagulation achieves effective and safe endoscopic hemostasis during wide-field endoscopic resection of large colonic lesions (with videos). *Gastrointest Endosc*. 2013; 78(1):158–163.e1. [PubMed: 23570622]
53. Jung M. The ‘difficult’ polyp: pitfalls for endoscopic removal. *Dig Dis*. 2012; 30(Suppl 2):74–80. [PubMed: 23207936]
54. Binmoeller KF, et al. “Underwater” EMR without submucosal injection for large sessile colorectal polyps (with video). *Gastrointest Endosc*. 2012; 75(5):1086–91. [PubMed: 22365184]
55. Wang AY, et al. Underwater endoscopic mucosal resection of colorectal neoplasia is easily learned, efficacious, and safe. *Surg Endosc*. 2014; 28(4):1348–54. [PubMed: 24232051]

56. Omata F, et al. Modifiable risk factors for colorectal neoplasms and hyperplastic polyps. *Intern Med.* 2009; 48(3):123–8. [PubMed: 19182421]
57. Terry MB, et al. Risk factors for advanced colorectal adenomas: a pooled analysis. *Cancer Epidemiol Biomarkers Prev.* 2002; 11(7):622–9. [PubMed: 12101109]
58. Aune D, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. *BMJ.* 2011; 343:d6617. [PubMed: 22074852]
59. Clark JC, et al. Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. *Int J Cancer.* 1985; 36(2):179–86. [PubMed: 4018911]
60. Kearney J, et al. Diet, alcohol, and smoking and the occurrence of hyperplastic polyps of the colon and rectum (United States). *Cancer Causes Control.* 1995; 6(1):45–56. [PubMed: 7718735]
61. Martínez ME, et al. A case-control study of dietary intake and other lifestyle risk factors for hyperplastic polyps. *Gastroenterology.* 1997; 113(2):423–9. [PubMed: 9247459]
62. Shrubsole MJ, et al. Alcohol drinking, cigarette smoking, and risk of colorectal adenomatous and hyperplastic polyps. *Am J Epidemiol.* 2008; 167(9):1050–8. [PubMed: 18304959]
63. Schreiner MA, Weiss DG, Lieberman DA. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. *Gastroenterology.* 2010; 139(5):1497–502. [PubMed: 20633561]
64. Wallace K, et al. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. *Cancer Epidemiol Biomarkers Prev.* 2009; 18(8):2310–7. [PubMed: 19661090]
65. Burnett-Hartman AN, et al. Differences in epidemiologic risk factors for colorectal adenomas and serrated polyps by lesion severity and anatomical site. *Am J Epidemiol.* 2013; 177(7):625–37. [PubMed: 23459948]
66. Chia VM, et al. Risk of microsatellite-unstable colorectal cancer is associated jointly with smoking and nonsteroidal anti-inflammatory drug use. *Cancer Res.* 2006; 66(13):6877–83. [PubMed: 16818666]
67. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. *Lancet Oncol.* 2012; 13(5):518–27. [PubMed: 22440112]
68. Burn J, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet.* 2011; 378(9809):2081–7. [PubMed: 22036019]
69. Kawasaki T, et al. Cyclooxygenase-2 overexpression is common in serrated and non-serrated colorectal adenoma, but uncommon in hyperplastic polyp and sessile serrated polyp/adenoma. *BMC Cancer.* 2008; 8:33. [PubMed: 18230181]
70. Nishihara R, et al. Aspirin use and risk of colorectal cancer according to BRAF mutation status. *JAMA.* 2013; 309(24):2563–71. [PubMed: 23800934]
71. Liao X, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med.* 2012; 367(17):1596–606. [PubMed: 23094721]
72. Rosty C, et al. Phenotype and polyp landscape in serrated polyposis syndrome: a series of 100 patients from genetics clinics. *Am J Surg Pathol.* 2012; 36(6):876–82. [PubMed: 22510757]
73. Cathomas G. PIK3CA in Colorectal Cancer. *Front Oncol.* 2014; 4:35. [PubMed: 24624362]
74. Bouwens MW, et al. Simple clinical risk score identifies patients with serrated polyps in routine practice. *Cancer Prev Res (Phila).* 2013; 6(8):855–63. [PubMed: 23824513]
75. https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf
76. Vu HT, et al. Individuals with sessile serrated polyps express an aggressive colorectal phenotype. *Dis Colon Rectum.* 2011; 54(10):1216–23. [PubMed: 21904135]
77. Snover, D.; Ahnen, DJ.; Burt, RW.; Odze, RD. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman, FT.; Carneiro, F.; Hruban, RH.; Theise, ND., editors. *WHO Classification of Tumours of the Digestive System.* LYON: IARC; 2010. p. 160-5.
78. Biswas S, et al. High prevalence of hyperplastic polyposis syndrome (serrated polyposis) in the NHS bowel cancer screening programme. *Gut.* 2013; 62(3):475. [PubMed: 22851664]

79. Boparai KS, et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. *Gut*. 2010; 59(8):1094–100. [PubMed: 19710031]
80. Kalady MF, et al. Defining phenotypes and cancer risk in hyperplastic polyposis syndrome. *Dis Colon Rectum*. 2011; 54(2):164–70. [PubMed: 21228663]
81. Hyman NH, Anderson P, Blasyk H. Hyperplastic polyposis and the risk of colorectal cancer. *Dis Colon Rectum*. 2004; 47(12):2101–4. [PubMed: 15657661]
82. Boparai KS, et al. Increased colorectal cancer risk in first-degree relatives of patients with hyperplastic polyposis syndrome. *Gut*. 2010; 59(9):1222–5. [PubMed: 20584785]

Figure 1. Proposed Serrated Pathway to Colorectal Cancer

Normal colonic crypts have regular test-tube like crypts with a smooth lumen. Hyperplastic polyps (HP) have serrations in the upper two-thirds of the crypt. In SSPs, serrations extend deeper into the crypt and the crypt base is often dilated and may have a boot or inverted “T” shape. SSPs with cytologic dysplasia (SSP-CD) have focal areas of conventional dysplasia (arrows) that are thought to rapidly progress to sporadic MSI-H CRCs. Modified from refs [3, 12, 13], photographs from Dr. Russell Nash.

Table 1

US Multi-Society Task Force on Colorectal Cancer (MSTF) Guidelines for Surveillance of Patients with Serrated Polyps [10]

Size/Histology of Serrated Polyp	Colonoscopy Surveillance Interval (years)
Small (<1cm) HPs in rectosigmoid	10
Small SSPs without dysplasia	5
Large (≥ 1cm) SSP without dysplasia *	3
Any SSP-CD	3
Any TSA	3
Serrated Polyposis Syndrome	1

Abbreviations: HP, hyperplastic polyp; SSP, sessile serrated polyp; SSP-CD, sessile serrated polyp with cytologic dysplasia; TSA, traditional serrated adenoma; SPS, Sessile Serrated Polyposis.

* Large (≥ 1 cm) proximal serrated polyps can be considered SSPs even if they are pathologically designated HPs.

Table 2

Sessile Serrated Polyposis Surveillance Guidelines

Organization	Probands Colonoscopy/Polypectomy	First Degree Relatives	
		Age to start (yrs)	Interval
MSTF [10]	Annual	Not Addressed	Not Addressed
NCCN [75]	1–3 years	Age 40 <i>or</i> At time of earliest SPS diagnosis in the family <i>or</i> 10 yrs before earliest CRC in the family (whichever is earlier)	5 years <i>or</i> 1–3 years if SSPs or adenomas found
Rex et al [3]	Annual	Age 40 <i>or</i> 10 yrs before earliest CRC in the family (whichever is earlier)	5 years <i>or</i> Less if polyps found

Abbreviations: MSTF, US Multi-society Task Force on GI Cancer; NCCN, National Comprehensive Cancer Network.