Sessile Serrated Adenomas: An Evidence-Based Guide to Management

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The concept of serrated colorectal neoplasia and a serrated pathway to colorectal cancer (CRC) is relatively new and continuing to evolve, but it has become highly relevant to gastroenterologists, pathologist, and oncologists alike. Sessile serrated adenomas (SSA) are now thought to be the major precursor lesion of serrated pathway cancers, which represent up to one-third of all sporadic CRC cases. However, despite their increasingly recognized importance, relatively little is known about the epidemiology and natural history of SSAs, and the molecular and epigenetic aspects are incompletely understood. Endoscopists must be aware of the unique features of SSAs so that the practice of colonoscopic screening for CRC can include optimized detection, removal, and appropriate surveillance of SSAs and other serrated precursor lesions. In this review, we discuss the history, epidemiology, and pathologic aspects of SSAs, as well as a recommended management approach and a discussion of uncertainties and opportunities for future research.

Keywords: Sessile Serrated Adenoma; Sessile Serrated Polyp; Serrated Neoplasia; Colorectal Cancer Screening; Colonoscopy; Endoscopic Detection; Polypectomy.

Colorectal cancer (CRC) kills more than 600,000 people annually worldwide, and is the second leading cause of cancer death in the United States.1,2 Until recently, adenomatous polyps (now referred to as conventional adenomas) were considered the precursor lesions of all cases of sporadic colon cancer, which was thought to occur via a series of well-defined molecular genetic steps along the chromosomal instability pathway.3

Recent research has indicated that this paradigm does not pertain to all sporadic CRC.4 Previously, all hyperplastic colorectal polyps were regarded as relatively harmless lesions without malignant potential. It is now recognized that these polyps are in fact a heterogeneous group, now called serrated polyps, characterized primarily by a saw-toothed appearance of colonic crypts. This group includes premalignant lesions such as the sessile serrated adenoma (SSA) (also known as the sessile serrated polypl or lesion) and the traditional serrated adenoma (TSA), in addition to the more innocuous hyperplastic polypl (HP).5 SSAs are the prototypical precursor lesions of the “serrated pathway” to colorectal cancer (CRC), now understood to have the potential to develop into sporadic CRCs via a series of molecular alterations including BRAF mutation and CpG island methylation, with epigenetic inactivation of the mismatch repair gene MLH1 resulting in microsatellite instability (MSI) (Figure 1).5,9 SSAs are probably the precursor to CpG island methylator phenotype (CIMP) high microsatellite stable (MSS) carcinomas as well.10 SSAs are a furtive foe for both the gastroenterologist and pathologist. They tend to be proximally located, have subtle endoscopic features, and are susceptible to being both overlooked and incompletely resected by endoscopists. To complicate matters further, there remains considerable interpathologist variability in the diagnosis of serrated polyp subtypes. These features and their potential to progress may explain (at least in part) why colonoscopy offers less protection from right-sided CRC.11–13 In addition, interval CRCs (ie, those occurring after a previous colonoscopy) frequently are located in the proximal colon and have molecular features of serrated pathway cancers such as CIMP and MSI, suggesting that SSAs contribute to this problem as well (Figure 2).13–16 Serrated pathway cancers are thought to be responsible for 20% to 35% of CRC cases,4,17 which makes this CRC subtype a substantial public health problem, with an incidence potentially greater than that of pancreatic, gastric, or esophageal cancer.2

Given their potential public health importance, this review focuses on SSAs, with particular attention to

Abbreviations used in this paper: CI, confidence interval; CIMP, CpG island methylator phenotype; CRC, colorectal cancer; CT, computed tomography; FIT, fecal immunochemical testing; HP, hyperplastic polypl; MSI, microsatellite instability; MSS, microsatellite stable; MVHP, microvesicular hyperplastic polypl; OR, odds ratio; PSP, proximal serrated polypl; SPS, serrated polypl syndrome; SSA, sessile serrated adenoma; SSAD, sessile serrated adenomas with dysplasia; TSA, traditional serrated adenoma; WHO, World Health Organization.
clinical aspects relevant to gastroenterologists. A number of reviews have been published on the pathologic aspects of these lesions,\textsuperscript{6–8,17} and these aspects are covered only briefly here.

### History

The understanding of serrated polyps has been evolving over the past 30 years. Originally, all such lesions were classified as HPs, and considered benign, non-neoplastic colorectal polyps, in contrast to adenomatous polyps (ie, conventional adenomas). Occasional reports in the 1970s and 1980s challenged the convention that HPs lacked malignant potential,\textsuperscript{18–21} but it was not until the 1990s when the term “serrated adenoma” was coined by Longacre and Fenoglio-Presier\textsuperscript{22} to describe a polyp with crypt serration resembling that of HPs, but also with cytologic dysplasia not characteristic of HPs. A number of these serrated adenomas (which would be classified as TSAs using contemporary terminology) had foci of intramucosal carcinoma, establishing a risk of neoplastic transformation, and thus this report served to codify the premalignant potential of some serrated lesions. In 1996, Torlakovic and Snover\textsuperscript{23} analyzed polyps from persons with HPs (now known as serrated polyposis, defined later), and identified a previously unrecognized serrated polyp characterized by large size and proximal location, and histologically by architectural distortion resulting from abnormalities in proliferation (Figure 1). This is generally considered the first description of the SSA, although this nomenclature was not generally acknowledged until a 2003 report that described TSAs and SSAs as separate entities.\textsuperscript{24} Subsequent reports have helped to refine the pathologic and molecular features of SSAs.\textsuperscript{8,25,26}

### Taxonomy and Nomenclature

The World Health Organization (WHO) now recognizes 3 categories of serrated polyps, all characterized by serration of the glandular epithelium: HPs, SSAs, and TSAs (Supplementary Figure 1).\textsuperscript{27}

![Figure 1. Proposed serrated pathway to MSI CRC, with characteristic crypt alterations, histologic and endoscopic appearance, and epigenetic and genetic alterations. Dotted line between MVHP and SSA indicates a possible but unproven progression step. Regarding crypt alterations, the thickened line indicates a proliferative zone, which is expanded in HPs, and migrates upward in SSAs. Arrows indicate the direction of maturation. See text for details. MSI-H, high microsatellite instability. Modified with permission from Snover et al.\textsuperscript{17}](image-url)
Hyperplastic Polyps

HPs are typically small (<5 mm), and roughly 70% are located in the distal colon and rectum.28,29 Endoscopically, or whitish color, sessile or flat morphology, and have a type II asteroid, stellate, or papillary Kudo pit pattern when examined with chromoendoscopy or narrow-band imaging.30 Histologically, HPs have crypt serration involving the upper segment of colonic crypts, with normal proliferation and no nuclear atypia or dysplasia.26 HPs are the most common type of serrated polyp, representing 29% to 40% of all polyps, and 80% to 95% of all serrated polyps.24,31,32 There are several subtypes of HPs including the most common microvesicular hyperplastic polyp (MVHP), the goblet cell–rich HP, and the mucin-poor HP (Supplementary Figure 1). Although HPs as a group do not directly progress to malignancy, some MVHPs do contain a BRAFV600E mutation, which disrupts normal apoptosis of epithelial cells.33 MVHPs also have a higher incidence of CIMP, especially in the proximal colon, a trait it shares with SSAs.33 For these reasons, it has been proposed that MVHPs may progress to SSAs, but this has not been proven.34

Figure 2. SSAs likely contribute to the problem of interval (or postcolonoscopy) cancers for 3 chief reasons: (1) SSAs can be difficult to detect during colonoscopy and are commonly missed; (2) it is thought that SSAs have the potential for rapid progression owing to the development of MSI, especially after dysplasia develops; and (3) incomplete polypectomy is common with SSAs. Hollow arrows represent potential targets for combating this problem.

Sessile Serrated Adenomas

SSAs are significantly less common than HPs. Depending on the series, SSAs represent up to one fifth of all serrated polyps.32,35–37 There remains considerable controversy as to the best name for this lesion (Table 1). Some investigators prefer the term sessile serrated polyp to differentiate it from conventional adenomas, whereas other investigators (particularly in Europe) prefer the term sessile serrated lesion because SSAs can be nonpolypoid and flat. Although SSA (and TSA) contain the word “adenoma,” it is important to recognize that these lesions are quite distinct from conventional adenomas with respect to histology and molecular biology. Conventional adenomas by definition contain dysplasia, but SSAs typically are
nondysplastic. The characteristic histology, molecular features, epidemiology, and endoscopic appearance of SSAs will be described further later.

**Traditional Serrated Adenomas**

TSAs are the least common serrated lesions, representing only 1% of these polyps. TSA tend to be left sided, protuberant, and/or pedunculated, and a significant proportion harbor conventional dysplasia. Histologically, TSA have villiform features and cells with elongated nuclei and eosinophilic cytoplasm along with ectopic crypts. Given their rarity, these polyps and their behavior are not as well characterized as HPs and SSAs. Although TSA also have malignant potential, their pathway to cancer involves different steps than SSAs, and is not as well understood. In contrast to SSAs, TSA are more commonly KRAS-mutated (vs BRAF-mutated), may show epigenetic inactivation of other DNA repair genes such as O6-methylguanine-DNA methyl-transferase (MGMT), and likely give rise to MSS cancers. Furthermore, because TSA have an endoscopic appearance similar to conventional adenomas and typically are located distally, they do not present the same challenges as SSAs with respect to endoscopic detection, and are unlikely to be overlooked. TSA are also less likely to be misclassified pathologically as HPs.

**Serrated Polyposis Syndrome**

Serrated polyposis syndrome (SPS) (formerly known as hyperplastic polyposis) is a condition of multiplicity of serrated polyps. The serrated polyps found in patients with SPS include mainly SSAs, but HPs also are present, in addition to occasional TSA. Conventional adenomas also can co-exist with serrated lesions in SPS and the presence of adenomas may portend an increased CRC risk in syndromic patients. The mean age at presentation is approximately 55 years, and males and females are affected equally. Although some cases may be heritable, the exact genetic defect associated with SPS has not yet been identified, and the

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**Table 1. Nomenclature Issues of SSA**

<table>
<thead>
<tr>
<th>Proposed term</th>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>SSA</td>
<td>Term adenoma connotes premalignant potential</td>
<td>Creates confusion with conventional adenomas for providers and patients</td>
</tr>
<tr>
<td></td>
<td>Term differentiates SSAs from HPs</td>
<td>Some SSAs are flat and nonpolypoid by Paris classification</td>
</tr>
<tr>
<td></td>
<td>Avoids confusion with conventional adenomas</td>
<td>Fails to convey the premalignant potential of these lesions</td>
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<td></td>
<td>Does not imply dysplasia is present</td>
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<td>Sessile serrated polyp</td>
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<td>Sessile serrated lesion</td>
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<tr>
<td>SSA/P</td>
<td>Hybrid term of SSA and sessile serrated polyp indicates that both terms apply to same lesion</td>
<td>Cumbersome</td>
</tr>
<tr>
<td></td>
<td>Most inclusive term</td>
<td></td>
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<tr>
<td>Serrated adenoma</td>
<td>Congruent with terminology of other premalignant colon polyps (eg, tubular adenomas, villous adenomas)</td>
<td>Nonspecific term could include both SSAs and TSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of this term is discouraged</td>
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<tr>
<td>Serrated polyp with abnormal proliferation</td>
<td>Indicates that lesions have abnormal proliferation even in absence of true dysplasia</td>
<td>Nonspecific term could include both SSAs and TSA</td>
</tr>
<tr>
<td>Giant HP</td>
<td>Historical importance (first term used by Jass)</td>
<td>Does not differentiate from HP apart from size</td>
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<tr>
<td></td>
<td>Indicates large size</td>
<td>Does not connote premalignant potential</td>
</tr>
<tr>
<td></td>
<td>Differentiates from diminutive HPs</td>
<td>Some SSAs are small</td>
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<tr>
<td>Variant HP</td>
<td>Differentiates from typical HPs</td>
<td>Suggests SSAs are a subset of HPs</td>
</tr>
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SSA/P, sessile serrated adenoma or polyp.
pattern of inheritance is uncertain. Therefore, the diagnosis currently is based on meeting somewhat arbitrary clinical criteria. According to the WHO, persons may be diagnosed with SPS if they have the following findings on a single colonoscopic screening examination: (1) at least 5 serrated polyps proximal to the sigmoid colon, 2 of which are greater than 10 mm in diameter; (2) any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; or (3) more than 20 serrated polyps of any size distributed throughout the colon. Patients with SPS generally are considered to be at increased risk of CRC. Case series of patients with SPS have reported that between 25% and 70% of SPS patients have CRC at the time of initial diagnosis or during follow-up evaluation. However, such studies are prone to referral bias, and some studies report no associated cancer risk, and therefore the actual risk of malignancy associated with SPS is unknown.

### Histopathology

SSAs are characterized by distorted crypt bases and crypt dilation caused by migration of the proliferative zone to the side of the crypt. These features distinguish SSAs from HPs, which have a normal basal proliferative zone and straight (although serrated) crypts (Figure 1). Unlike conventional adenomas, SSAs do not typically have overt cytologic dysplasia, although dysplasia does develop in some lesions as they progress. It is important to note that the dysplasia found in SSAs has different molecular features than the dysplasia seen in conventional adenomas, and hence SSAs with cytologic dysplasia are not simply a combined SSA/tubular adenoma. SSAs also can have foci of intramucosal carcinoma and/or adjacent invasive CRC.

### Genetics and Epigenetics

The pathway by which conventional adenomas give rise to CRC has been well studied and involves mutations in APC, KRAS, and p53 among others, whereas the molecular alterations associated with SSAs include BRAF mutation, and CIMP, which can lead to epigenetic silencing of MLH1, a mismatch repair gene, resulting in MSI (Figure 1). In contrast, BRAF mutations are extremely rare in conventional adenomas. There is heterogeneity among serrated lesions, however; some CIMP-positive serrated lesions lead to MSS cancers, possibly owing to methylation of MGMT, tumor suppressors, or apoptosis genes. In line with their distinct genetic and epigenetic profile is a corresponding difference in behavior of SSAs compared with conventional adenomas. Because serrated pathway cancers can involve MSI, it is thought that they have the potential for rapid growth once cytologic dysplasia has developed, although this is difficult to prove definitively. However, the clinical consequences of specific epigenetic alterations found in SSAs are largely unstudied.

### Epidemiology

The understanding of the epidemiology of SSAs is in evolution. Most studies of the epidemiology of serrated polyps predate the contemporary understanding of serrated neoplasia. The early investigations of HPs are really studies of what we now know to be serrated polyps in general, which may have included some SSAs. Nevertheless, more recent studies have begun to focus on risk factors of significant serrated polyps (eg, large and/or right-sided polyps) and SSAs specifically.

#### Prevalence

Approximately 20% to 40% of adults have at least 1 serrated polyp, including distal HPs. SSAs represent 3% to 22% of serrated lesions, and 75% to 90% of SSAs are right sided. In average-risk screening patients, the reported SSA prevalence ranges from 2% to 7%. A study that used high-resolution magnifying chromoendoscopy to optimize detection and included some high-risk patients (ie, personal or family history of CRC or polyps) reported the prevalence of SSAs was as high as 14%. Other investigators using surrogate definitions for significant serrated lesions (eg, large or proximally located serrated polyps) have reported prevalence estimates in the 2% to 20% range in average-risk screening populations. A number of pathology series focused on serrated lesions also have been reported in which, typically, colorectal polypectomy specimens from a particular pathology laboratory are reviewed using current pathologic criteria. From these series, it is estimated that SSAs represent 1% to 9% of all resected colorectal polyps. Multiplicity of serrated polyps is common. A recent study of more than 1000 patients with serrated polyps (including HPs, SSAs, and TSAs) reported that 44% of patients with serrated polyps had more than 1 serrated polyp, including 21% with 2 serrated polyps, 10% with 3 serrated polyps, 5% with 4 serrated polyps, and 8% with 5 or more serrated polyps.

#### Risk Factors

A number of studies have examined the epidemiology and risk factors of HPs as a group, but because small distal HPs represent the majority of serrated polyps, the significance of these findings with respect to SSAs is questionable. Although the risk factors for SSAs and HPs likely overlap to some degree, it is important to understand factors that predispose persons to develop SSAs specifically. As a surrogate for SSAs, some investigators have examined the epidemiology of proximally located or...
large (typically 1 cm or larger) serrated polyps. Proximal serrated polyps (PSP) have been associated with tobacco use in some studies,28,59 but not others.60 Nonsteroidal anti-inflammatory drug use also has been associated with a decreased risk of PSPs.39,60

With regard to SSAs specifically, the published research on risk factors is limited. Several studies have identified tobacco as a risk factor for SSAs.51–63 There have been mixed results with respect to obesity because one study did find an association between increased body mass index and SSAs,61 however, 2 other studies did not.60,62 Although conventional adenomas are consistently more common in men, this does not appear to be true of SSAs. Colonoscopic series have reported that SSAs are at least as common in women as they are in men, with women representing 50% to 63% of those with detected SSAs.37,62 Similarly, pathology series report that 49% to 65% of those with removed SSAs are women.51,32,36,37,61,64,65 Interestingly, one study reported that women comprised progressively higher proportions of those with more advanced serrated lesions (women represented 53%, 57%, 69%, and 76% of those with nondysplastic SSAs, SSAs with low- and high-grade dysplasia, and SSAs with invasive adenocarcinoma, respectively).31 One US study reported an association between higher levels of education and SSAs.62 Further research is needed to clarify whether other factors such as race, alcohol intake, other socioeconomic factors, and diet are potentially significant risk factors for the development of SSAs. Identifying predisposing factors for these important CRC precursors is important for prevention and diagnostic efforts.

Recently, a risk score for identifying large, proximal, or dysplastic serrated polyps has been reported.29 This risk score was based on associated factors identified in a cross-sectional analysis of individuals undergoing elective colonoscopy at a single Dutch hospital. The identified predictive factors based on multivariate analysis included age older than 50 (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.3–3.8), history of serrated polyps (OR, 2.6; 95% CI, 1.3–4.9), current smoking (OR, 2.2; 95% CI, 1.4–3.6), and lack of regular nonsteroidal anti-inflammatory drug use (OR, 1.8; 95% CI, 1.1–3.0). It remains to be seen whether this score will be useful in clinical practice, but it does serve to emphasize that the risk profile for SSAs differs somewhat from that of conventional adenomas (eg, lack of association with male sex), and endoscopists should be especially vigilant for SSAs in certain groups of patients (eg, smokers and those with a history of SSAs).

**Natural History**

**Risk of Dysplasia and Progression**

The risk and rate of progression of SSAs is not well documented. Some investigators have postulated that SSAs arise from serrated aberrant crypt foci and/or precursor HPs (namely MVHP), but it also is possible that they arise de novo (Figure 1).5,17,66,67 As mentioned earlier, cytologic dysplasia is not common in SSAs, although they do have malignant potential. In one large cross-sectional study of 2416 SSAs, 85% were nondysplastic, 14% had low- or high-grade dysplasia, and 1% had adenocarcinoma.31 In addition, there have been case reports of rapid progression of SSAs to cancer in less than 1 year.4

**Synchronous Neoplasia**

Although the risk of synchronous neoplasia for SSAs specifically has not been well studied, there is some evidence that proximal and large serrated polyps are associated with an increased risk of synchronous advanced neoplasia and cancer.54,58,64,68,69 Furthermore, persons with concomitant SSAs and conventional adenomas appear to be at high risk of synchronous CRC.64 Persons with SSAs also frequently have synchronous serrated polyps.70

**Metachronous Neoplasia**

A few studies have suggested that SSAs and large HPs may be associated with an increased risk of metachronous polyps,58,65,71 but these studies generally used outdated pathologic criteria to define the serrated lesions, were not confined specifically to SSAs, or were limited by small sample size and variable follow-up periods. Further research is needed to better quantify the risk of synchronous and metachronous neoplasia associated with SSAs specifically.

**Detection and Removal**

**Endoscopic Appearance**

Characteristic features of SSAs include proximal location (>75%),32,36 sessile or flat morphology (>90%),39,72 a resemblance to prominent folds (37%),72 pale color (75%),39 indistinct borders (73%),73 and mucus capping (64%–100%)72,74 (Figure 3). All of these features contribute to a subtle endoscopic appearance, and thus without careful attention from the endoscopist, even large SSAs can escape detection. In 20% to 50% of SSAs, a rim of bubbles or debris is present that can help delineate the lesions and serve as an identification aid.72 On chromoendoscopy or narrow-band imaging, SSAs typically have a type II-0 or open Kudo pit pattern on a magnified view.40 Several Japanese studies have reported this pit pattern has good sensitivity and specificity for identifying SSAs (84%–97% and 66%–86%, respectively), but this technique is highly operator-dependent.75,75,76
**Procedural Factors**

**Bowel preparation.** It is well established that inadequate bowel preparation negatively impacts adenoma detection, particularly for smaller lesions.\(^{77}\) SSAs are likely even more vulnerable to underdetection in persons with suboptimal preparations. There are multiple reasons for this problem: (1) flat morphology makes SSAs more vulnerable to being obscured by adherent stool and intestinal fluids; (2) SSAs more commonly are located in the right colon, which is more susceptible to imperfect cleansing; and (3) the mucus cap and ring of debris surrounding SSAs often facilitates identification in well-prepared colons, so poor preparations (and water jet irrigation needed to combat them) may eliminate this identification tool. Better bowel preparation is associated with improved detection of flat lesions in general,\(^{78}\) but one recent study did not find a statistically significant association between bowel preparation and PSP detection.\(^{56}\) However, the effects of bowel preparation on detection of SSAs specifically has not been well studied.

**Endoscopic technique.** Different investigators have reported various techniques to optimize the detection of proximally located polypos including intensive inspection or second looks in the right colon, examination with narrow-band imaging, routine retroflexion in the ascending colon, cap-fitted colonoscopy, and spray chromoendoscopy.\(^{79-83}\) However, data that these techniques improve detection of SSAs specifically are lacking. Nevertheless, it makes intuitive sense that more careful and thorough examination of the right colon will help to optimize SSA detection. In addition, high rates of SSA detection have been reported with high-resolution magnified chromoendoscopy and use of pit-pattern recognition as mentioned earlier.\(^{12}\) However, there is significant variability in endoscopists’ abilities to accurately identify pit patterns, neither routine chromoendoscopy nor endoscopic magnification is in widespread use currently in the United States, and the cost effectiveness of these techniques in average-risk screening populations is questionable.\(^{84}\)

**Withdrawal time.** Longer withdrawal time during colonoscopic screening has been linked with higher detection rates of conventional adenomas.\(^{85}\) However, the existing data linking withdrawal times to serrated polyyp detection are relatively sparse. One retrospective US study of more than 18,000 colonoscopies reported a strong relationship between withdrawal time and overall serrated polyyp detection.\(^{86}\) More recently, a prospective Dutch study found that longer withdrawal time was associated with significantly better PSP detection (OR, 1.12; 95% CI, 1.10–1.16).\(^ {56}\) However, these studies were limited by the small number of endoscopists, and further research is needed on this topic.

**Endoscopic Detection Rates**

Several studies have documented a wide variability in endoscopists’ detection of PSPs and SSAs specifically.\(^{77,55}\) Hetzel et al\(^ {37}\) reported results from a single-center retrospective cohort study of 7192 patients undergoing average-risk CRC screening colonoscopies by 13 different endoscopists. In this study, SSA detection ranged from 0% in the lowest detector to 2.2% in the highest detector. Interestingly, this same study reported that overall SSA detection improved substantially over time, from 0.2% in 2006 to 1.1% in 2008, suggesting either increased recognition by endoscopists, pathologists, or both, over this time period. Kahi et al\(^ {55}\) also investigated endoscopic detection of serrated lesions in a single-center retrospective study of 6681 patients undergoing average-risk CRC screening by 15 different endoscopists. In this study, detection of PSPs ranged from 1% to 18% for individual endoscopists. In a prospective study of 1426 people undergoing colonoscopic screening, de Wijkerslooth et al\(^ {56}\) reported that the PSP detection rate ranged from 6% to 22% among 5 different experienced endoscopists. Another single-center (and single endoscopist) study reported detection of PSPs and/or SSAs in 23% of screening colonoscopies after using specialized lesion-recognition training, cap-fitted colonoscopy, rigorous cleansing, and intensive inspection.\(^ {82}\) Several of these studies reported that SSA (or PSP) detection generally correlated with adenoma detection rates.\(^ {37,55}\) It is clear from these data that when performed skillfully, endoscopy can identify important serrated lesions quite commonly. Distressingly, these data also highlight the fact that some endoscopists do not identify SSAs...
commonly enough, a situation that likely is fairly pervasive throughout the gastroenterology profession. Individual and practice improvement strategies are needed to reduce this variation and improve the detection and removal of important serrated precursor lesions on an individual and systematic level.

**Detection of Sessile Serrated Adenomas by Other Methods**

Although colonoscopy certainly is imperfect, it likely is superior to alternative CRC screening methods for the detection of SSAs. Little has been published in this area, but it is known that computed tomography (CT) colonography has difficulty detecting flat and sessile lesions because of its reliance on morphology, and absence of information on surface characteristics (color, vascular pattern, and so forth).87,88 There are scant data on the detection of lesions other than conventional adenomas by CT colonography, but what has been published suggests that this technique lacks adequate sensitivity for these lesions.89 With respect to fecal occult blood testing and fecal immunochemical testing (FIT), serrated polyps are thought to be less likely to hemorrhage than conventional adenomas, so screening tests that rely on the detection of blood are unlikely to be very effective.90,91 The recent development of stool DNA tests for CRC largely have focused on markers based on the traditional adenoma-carcinoma sequence (ie, APC, KRAS), but these tests offer some promise of serrated polyp detection, particularly if methylated or other markers of the serrated pathway are included.91,92 However, there is a paucity of published data on SSA detection with fecal occult blood testing, FIT, and stool DNA panels because, for the most part, serrated lesions have been ignored in CRC screening trials. Therefore, with all of its limitations, colonoscopy likely represents our best chance of addressing and removing serrated pathway precursor lesions such as SSAs.

**Endoscopic Removal**

Few published studies have addressed the issue of optimal SSA polypectomy technique. In one recent study, resections of 346 polyps (including 42 SSAs) were examined for completeness using standardized post-polypectomy biopsy specimens from the resected margins.93 This study found that 31% of SSAs were resected incompletely, compared with 7% of other polyps. More strikingly, nearly half (48%) of the large SSAs (between 1 and 2 cm) were resected incompletely. This alarmingly high rate of incomplete resection of SSAs highlights the need for extra care when resecting large flat polyps in the right colon to avoid residual polyp tissue. Incomplete resection of polyps is a likely explanation for some interval cancers (Figure 2).94

**Pathologic Interpretation**

Because serrated neoplasia is a recent concept, pathologic interpretation also is inconsistent. One report from a single academic center with 12 different pathologists reported that the SSA classification prevalence varied from 0% to 4% of patients depending on the pathologist.55 Other studies of tandem pathologist readings have shown variable interobserver agreement between pathologists, ranging from poor to good ($\kappa = 0.16–0.66$), with a substantial number of polyps read as an SSA by one pathologist, and as an HP by another.31,70,95 Further evidence of pathologic misclassification was provided by a recent Canadian study in which previously reported HPs were re-reviewed from a city-wide sample by 2 gastrointestinal pathologists according to current criteria.52 In this study, 17% of proximal HPs and 20% of HPs greater than 5 mm were reclassified as SSAs. For these reasons, some investigators advocate treating all right-sided and larger ($\geq 1$ cm) HPs the same as SSAs with respect to surveillance recommendations.96 However, gastrointestinal pathologists generally have higher reported SSA classification rates than nonspecialists,37,52 and a recent European study showed excellent agreement among expert pathologists ($\kappa >0.8$) regarding serrated lesions.97 In addition, there is evidence that pathologic diagnoses of SSAs have increased steadily in recent years.98 Taken together, these studies indicate that variation in pathologist interpretation may be reduced as the concept of serrated neoplasia becomes better understood and disseminated.

**Proposed Management**

Over the past several decades, colonoscopic screening in the United States has been tailored to the detection, removal, and surveillance of conventional adenomas. SSAs have received considerably less attention until recently. The problem of serrated neoplasia and SSAs specifically highlights many of the weaknesses of our current colonoscopy screening approach to CRC prevention (Figure 4). Indeed, there are data that prior colonoscopy offers little or no protection from SSAs, in contrast to advanced adenomas.99 From a public health standpoint, gastroenterologists must direct their attention to the optimal detection, removal, and appropriate surveillance of SSAs to effectively prevent sporadic CRC. From a patient-care standpoint, endoscopists must be aware of the existence, importance, and identifying features of SSAs to optimize the management of patients harboring these premalignant lesions. Ongoing professional education is important in this regard because this is a burgeoning area of research, and suggested management likely will be in evolution for the foreseeable future. Specific recommendations are provided later.
Educate Your Patients About Bowel Preparation

As discussed earlier, adequate purgative preparation before colonoscopy is critical to providing high-quality endoscopic screening for adenomas, flat lesions, and (likely) SSAs. There are now good data to support the use of split-dose preparation regimens, which are associated with better patient satisfaction, better colonic cleansing (particularly in the right colon), and improved adenoma and total polyp detection rates. Therefore, we currently recommend using split-dose preparation regimens for optimization of both conventional adenoma and serrated polyp detection.

Know Your Sessile Serrated Adenoma or Proximal Serrated Polyp Detection Rate

Given the known variation in endoscopic detection of SSAs, endoscopists should be aware of their SSA (or PSP) detection rate. Although there are data that SSA/PSP detection rates and adenoma detection rates are correlated, these are not equivalent; the endoscopists with the highest adenoma detection rates do not always have the highest SSA or PSP detection rates. Moreover, greater endoscopy experience does not necessarily imply a high PSP detection rate. Recognizing SSAs and other nonpolypoid and flat neoplastic lesions requires an overlapping yet distinct skill set than that required to detect polypoid adenomas. Nevertheless, it goes without saying that all endoscopists should strive to meet and exceed published standards for conventional adenoma detection rates. One group has suggested a target PSP detection rate of at least 5% for average-risk screening colonoscopies. Although optimal or benchmark SSA detection rates have not yet been firmly established, existing data suggest that SSAs should be identified in at least 1% of screening colonoscopies. The true prevalence of SSAs is probably significantly higher than this figure, so even endoscopists meeting these arbitrary metrics likely can improve their detection rates. Some groups have reported use of standardized education modules or training programs to optimize the detection of flat and subtle lesions. Suboptimal SSA detection, especially if out of proportion to PSP detection, also may indicate discordance between local pathologist interpretation and current pathology recommendations and should prompt a discussion regarding the classification of serrated polyps with the interpreting pathologist.

Perform Attentive Colonoscopy

Meticulous colonoscopy technique is needed to optimize SSA detection. In particular, assiduous examination of the right colon is important given that the majority of SSAs are proximally located. The endoscopist must perform careful examination of colonic folds and
mucus-covered areas for associated mucosal abnormalities. In our own practice, we recommend that endoscopists learn to retroflex the endoscope and use this technique in the ascending colon to better visualize the backs of folds in the right colon. This practice has been shown to be safe and effective in experienced hands. If the removal of these types of polyps including stiffer snares, removing SSAs; certain snares may be more effective for and remove any residual polyp. The use of narrow-band imaging or chromoendoscopy techniques may facilitate the identification and delineation of SSAs, especially if the endoscopist is trained in pit-pattern recognition. When suspicious lesions or mucosal abnormalities are found it is important to accurately record their size and location so that the site can be re-assessed at a later date if needed. The need for surgical resection of SSAs, even in inexperienced hands, is relatively common. Most SSAs are smaller than 2 cm (average size, 5–7 mm) and can be resected safely and effectively at the time of a screening or surveillance colonoscopy. Optimal technique varies depending on the individual characteristics of the SSA. For flat lesions, submucosal injection often is useful to provide a cushion for resection, and to allow for better visualization and seating of the polypectomy snare. Chromoendoscopy and/or including a dye (eg, indigo carmine) in the submucosal injection fluid also can help better define the margins of the polyp and assist complete resection. Chromoendoscopy and/or including a dye (eg, indigo carmine) in the submucosal injection fluid also can help better define the margins of the polyp and assist complete resection. In light of the data showing an inordinately high incomplete resection rate for SSAs larger than 1 cm, it seems reasonable to tattoo such lesions and delineate SSAs, especially if the endoscopist is experienced hands.93 Most SSAs are free of residual neoplasia and that information can aid in follow-up recommendations.

Resect Carefully

As with any neoplastic colorectal polyp, complete resection is important to reduce the risk of dysplastic or cancerous tissue left in situ, and to avoid regrowth of neoplastic tissue at the polypectomy site. As discussed earlier, incomplete resection of SSAs, even in experienced hands, is relatively common.93 Most SSAs are smaller than 2 cm (average size, 5–7 mm) and can be resected safely and effectively at the time of a screening or surveillance colonoscopy. Optimal technique varies depending on the individual characteristics of the SSA. For flat lesions, submucosal injection often is useful to provide a cushion for resection, and to allow for better visualization and seating of the polypectomy snare. Chromoendoscopy and/or including a dye (eg, indigo carmine) in the submucosal injection fluid also can help better define the margins of the polyp and assist complete resection. In light of the data showing an inordinately high incomplete resection rate for SSAs larger than 1 cm, it seems reasonable to tattoo such lesions and delineate SSAs, especially if the endoscopist is inexperienced in performing endoscopic mucosal resection, or is uncomfortable removing a suspected SSA because of its morphology (eg, flat or laterally spreading), size (eg, >2 cm), or location (behind a fold, abutting the ileocecal valve, and so forth), referral to a colleague or center with appropriate advanced endoscopy expertise in complex polypectomies is recommended.106 If the endoscopist is inexperienced in performing endoscopic mucosal resection, or is uncomfortable removing a suspected SSA because of its morphology (eg, flat or laterally spreading), size (eg, >2 cm), or location (behind a fold, abutting the ileocecal valve, and so forth), referral to a colleague or center with appropriate advanced endoscopy expertise in complex polypectomies is recommended.106,109 The need for surgical resection of SSAs is rare, and reserved for very large and/or dysplastic SSAs, multiple SSAs, or those located in difficult locations (eg, appendiceal orifice).109

Talk With Your Pathologist Colleagues

As discussed earlier, there is known variation in pathologic interpretation of serrated polyps. Before the unique histopathologic features of SSAs were identified, these lesions generally were read by pathologists as HPs. It is likely that some systematic under-reading of SSAs continues to occur today. Gastroenterologists should have a discussion with their pathology colleagues regarding the concept of serrated neoplasia and should partner to discuss cases in which the endoscopic and pathologic determinations differ (eg, a large rightsided sessile polyp with typical endoscopic features of an SSA read as a HP). Providing relevant clinical information, en bloc resections, and properly orientated specimens also helps pathologists to interpret polyps accurately.110 If this is performed, the pathologist should be able to determine if the margins of the polyp are free of residual neoplasia and that information can aid in follow-up recommendations.

Be Aware of Surveillance Guidelines

A key question with respect to the management of patients with SSAs pertains to the recommended interval for surveillance colonoscopy. Several investigators and groups have published recommendations on surveillance of individuals with serrated polyps (Table 2). Most recently, the US Multisociety Task Force guidelines for surveillance after colonoscopic polypectomy recommended 1 to 5 years of follow-up evaluation of SSAs, depending on the number and size of lesions found, and the presence or absence of dysplasia.111 These guidelines largely mirror those for conventional adenomas. A consensus panel of international experts on serrated neoplasia also recently published similar, but more detailed, recommendations.96 Individual investigators also have made various recommendations regarding surveillance of these lesions that vary from 6 months to 10 years.5,17,64,91,112,113 Some current colonoscopy and CRC screening guidelines do not make any specific recommendations regarding surveillance intervals for those with serrated lesions, or recommend that management be analogous to that of conventional adenomas.114–116 We favor the consensus panel guidelines, given their more detailed management recommendations96 but it is important to recognize that surveillance recommendations for SSAs likely will be in evolution as our understanding of the behavior and significance of these lesions improves. One area of ambiguity relates to SSAs with dysplasia (SSAD), for which the consensus panel guidelines recommend a 1- to 3-year surveillance interval. Although a 3-year surveillance examination seems
applicable for patients with SSADs if complete resection was achieved, endoscopists should have a low threshold to perform repeat colonoscopy at a short interval (3–6 mo) for assessment of an SSAD polypectomy site when piecemeal resection was performed, or when residual polyp tissue is suspected on the basis of endoscopic appearance or pathology evaluation.

An important consideration is patients with suspected SPS, for whom the recommended surveillance interval is 1 year. It is worth noting that WHO criteria 1 and 3 for SPS (see earlier) are the most common phenotypes, and given that multiplicity of serrated polyps is common, both scenarios can be underdiagnosed, leading to inappropriately long (ie, >1 y) surveillance recommendations in such patients. Interestingly, in patients with a history of SSAs, some investigators recommend considering optimizing surveillance detection by use of chromoendoscopy. Furthermore, extending endoscopic surveillance beyond the traditional cut-off point of 75 years of age also has been recommended because of the presumed potential for rapid neoplastic growth. However, evidence to support the benefit of these recommendations currently is lacking.

### Uncertainties and Future Directions

#### Pathogenesis

The understanding of serrated neoplasia continues to advance, but many uncertainties remain. Further research is needed in the area of pathogenesis of serrated neoplasia, so the genetic and epigenetic steps along the serrated pathway to CRC (particularly for CIMP-MSS carcinomas) can be better delineated. Discovery of the fundamental cause of CIMP and uniformity in its definition would help clarify this important feature of the serrated pathway. In addition, further study of patients with SPS and its phenotypes and inheritance patterns offers the opportunity to identify the genetic basis of this hereditary syndrome. It is likely that these genes also would be relevant to sporadic serrated neoplasia and SSAs specifically. It also is possible that the current diagnostic criteria for SPS may become meaningless if the rate of recognition of SSAs continues to increase, and/or if more meaningful phenotypic patterns emerge.


**Epidemiology and Natural History**

Despite growing recognition of the problem of serrated neoplasia, as described earlier, the epidemiology and natural history of SSAs remain poorly understood. A better understanding of the risk factors for SSAs may help to determine not only which populations have the highest risk of harboring these lesions, but also could help inform studies of pathogenesis. There have been limited longitudinal studies of these lesions, and little is known about the dwell time, features associated with rapid growth or recurrence, and the true prognostic significance of finding SSAs on colonoscopy. As such, the current guidelines for the management of serrated lesions\(^\text{96,111}\) are based more on expert opinion rather than a substantial evidence base. Additional prospective studies are necessary to better inform clinical decision making and surveillance recommendations. Along those lines, some investigators have recommended randomized trials of SSA polypectomy and surveillance vs watchful waiting or serial biopsies to generate evidence regarding the benefits and harms of different management strategies.\(^\text{116}\) Furthermore, the clinical implications of genetic and epigenetic alterations of SSAs largely are unknown. It is possible that a more comprehensive semimolecular classification of colorectal polyps will help better risk-stratify patients in the future.\(^\text{17}\)

**Detection and Resection**

Because variable detection (and underdetection specifically) is so pervasive, it seems that initial efforts should be directed at improving endoscopic detection and removal with existing technologies, personnel, and infrastructure. However, because the detection of SSAs is affected disproportionately by the inherent technical limitations of visual inspection with standard white-light colonoscopy, novel or adjunctive approaches may be needed. Several existing endoscopic tools offer the potential to improve SSA detection including magnification chromoendoscopy,\(^\text{32}\) cap-fitted colonoscopy,\(^\text{82}\) and retroflexion in ascending colon\(^\text{80}\) as detailed earlier. In addition, emerging technologies such as wide-angle colonoscopy,\(^\text{119}\) use of the third eye retroscope,\(^\text{120}\) and others also are promising in this regard. However, more research is needed to determine whether these devices and techniques (alone or in combination) are effective, easily learned, practical, and cost effective with respect to improving SSA detection. As mentioned earlier, stool DNA tests do offer some promise of serrated lesion detection, particularly if serrated pathway markers are included. Endomicroscopy, spectroscopy, and molecular imaging also are intriguing developments that potentially could impact SSA detection in the future.\(^\text{121–123}\)

Furthermore, better quantitative estimates of SSA detection by alternative screening methods (eg, FIT, CT colonography, flexible sigmoidoscopy) are needed to fully understand the implications of SSAs for screening guidelines and test selection.

Because resection of SSAs often is inadequate,\(^\text{93}\) further research is needed to optimize complete resection of these lesions to mitigate the risk of polyp regrowth and interval cancers (Figure 2). It is worth noting that the currently available tools for polypectomy (eg, standard oval snares) largely were developed with polyoid adenomas in mind, and other snare shapes and polypectomy tools may need to be appropriated or developed to optimize resection of SSAs and other large and/or flat colonic lesions.

**Conclusions**

SSAs represent a new type of combatant in the war against CRC, and it is important for clinicians and researchers to understand their importance. These lesions undoubtedly play a role in interval cancer development (Figure 2). It is clear that unless gastroenterologists direct their attention to the detection, removal, and appropriate surveillance of SSAs, optimal prevention of sporadic CRC will not be possible. The current CRC screening approach also must adapt to address serrated neoplasia (Figure 4). Additional research is needed in this area, particularly with regard to pathogenesis, epidemiology, behavior, and endoscopic management of these important CRC precursors.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at [http://dx.doi.org/10.1016/j.cgh.2013.10.035](http://dx.doi.org/10.1016/j.cgh.2013.10.035).

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Supplementary Figure 1. WHO taxonomy of serrated polyps.