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Management of Serrated Polyps of the Colon

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Abstract

Purpose of Review: The purpose of this review is to summarize the management of serrated colorectal polyps (SPs), with a particular focus on the most common premalignant SP, sessile serrated adenoma or polyp (SSA/P). These lesions present a challenge for endoscopists with respect to detection and resection, and are also susceptible to pathologic misdiagnosis.

Recent Findings: Patients with SSA/Ps are at an increased risk of future colorectal neoplasia, including advanced polyps and cancer. Reasonable benchmarks for SP detection rates are 5–7% for SSA/Ps and 10–12% for proximal SPs. Certain endoscopic techniques such as chromoendoscopy, narrow band imaging, water immersion, and wide-angle viewing may improve SSA/P detection. Emerging endoscopic techniques such as underwater polypectomy, suction pseudopolyp technique, and piecemeal cold snare polypectomy are helpful tools for the endoscopist's armamentarium for removing SSA/Ps. Proper orientation of SSA/P specimens can improve the accuracy of pathology readings. Patients with confirmed SSA/Ps and proximal HPs should undergo surveillance at intervals similar to what is recommended for patients with conventional adenomas. Patients with SSA/Ps may also be able to lower their risk of future polyps by targeting modifiable risk factors including tobacco and alcohol use and high fat diets. NSAIDs and aspirin appear to be protective agents.

Summary: SPs and SSA/Ps in particular are important colorectal cancer precursors that merit special attention to ensure adequate detection, resection, and surveillance.

Keywords

Colorectal cancer prevention; colonoscopy; serrated polyps; quality metrics; polypectomy

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States.[1, 2] The vast majority of CRCs are thought to arise from precancerous polyps, of which there exist two main types: conventional adenomas and serrated polyps (SP). SPs are divided into hyperplastic polyps (HP), traditional serrated adenomas (TSA), and sessile serrated adenomas/polyps (SSA/P) with or without dysplasia.[3, 4] Around 15–30% of sporadic CRC develops from SPs via the serrated neoplasia pathways, which are distinct from the traditional adenoma-carcinoma sequence for conventional adenomas.[5–8] For SSA/Ps, this involves the development of BRAF mutation, followed by CpG island methylation (CIMP), leading to epigenetic methylation of the promoters of key regulatory and tumor suppressor genes. The inactivation of mismatch repair genes such as MLH1 ultimately leads to microsatellite instability, a feature associated with serrated pathway adenocarcinomas.[9]

The classification of SPs has evolved significantly over the past several decades. The notion that CRCs arise from conventional adenomas dates back to the 1920s.[10] Accompanying this belief was the supposition that all non-adenomatous polyps including “hyperplastic polyps” (a term that previous encompassed most SPs) were benign. The understanding that SPs may have malignant potential began in the 1990s. The term “serrated adenoma” was first coined in 1990 by Longacre and Fenoglio-Preiser to characterize a new type of premalignant lesion with a saw-toothed appearance of the colonic mucosa (akin to what is seen in HPs), but with cytological atypia, and in some cases dysplasia.[11] Subsequently Torlakovic and Snover in 1996 histologically distinguished SSA/Ps and TSAs.[7, 12] The WHO defines the current pathologic standards for the three general categories of SPs: HPs, SSA/Ps, and TSAs.[3] With this evolution in the understanding of the histopathology and behavior of SPs, there have been accompanying changes to the diagnosis and management of these important CRC precursors.

The past 10 years have seen numerous advances in the detection and resection of SPs, and this field continues to grow. This review will attempt to summarize what is known about the management of colorectal SPs, and give evidence-based recommendations. In particular, we will focus on the management of SPs, including risk/protective factors, endoscopic detection, detection via non-endoscopic tests, endoscopic resection, handling of the pathologic specimens, pathology interpretation, surveillance intervals, and management of serrated polyposis syndrome.

Epidemiology and Taxonomy

SPs are the second most common group of colorectal polyps behind conventional adenomas, making up about 40% of polyps visualized on colonoscopy.[13–17] The vast majority of SPs are HPs, which account for approximately 70–90% of all SPs.[15] TSAs are the rarest type of SP, only accounting for about 1%.[13] SSA/Ps make up about 10–20% of SPs.[14, 13] However, it should be noted that prevalence estimates for SSA/Ps are varied due to differences in endoscopic detection.[15] SSA/Ps and TSAs are both precursors for serrated pathway cancers. The focus of this review is on SSA/Ps, which are of particular interest

because they are the most commonly encountered premalignant SP, and the pathway by which SSA/Ps develop into CRCs is the most well understood. To better define the SP nomenclature, pathological criteria for each category of SP are detailed below. A comparison of the three types of SPs is presented in Table 1.

Hyperplastic Polyps

HPs are characterized by the presence of straight crypts that rise perpendicularly from the muscularis mucosa to the polyp surface. There is minimal or no cytological atypia. HPs are subdivided into microvesicular (MVHP), goblet cell (GCHP), and mucin-poor (MPHP) subtypes[18] based on the mucin content of the epithelial cells.[3] MVHPs are characterized by small droplet (microvesicular) mucin in the cytoplasm of the cells with or without a few scattered goblet cells, whereas GCHPs are predominantly composed of goblet cells. MPHPs are the rarest and have minimal amounts of cytoplasmic mucin.[3] HPs are the most common SP and are typically diminutive or small lesions located in the rectum and sigmoid colon. True HPs are considered benign lesions with minimal or no risk of progression. However, as noted below, there is considerable histologic overlap between HPs and SSA/Ps, which can lead to histopathologic misdiagnosis (i.e. SSA/Ps may be misread as HPs).

Sessile Serrated Adenomas/Polyps

The term SSA/P is synonymous with “sessile serrated adenoma”, “sessile serrated polyp”, or “sessile serrated lesion”.[19] SSA/Ps are diagnosed using specific features, including deep crypt serration, crypt dilation, abnormally shaped crypt bases such as L or inverted T shapes, irregular distribution of crypts, and branched crypts. By WHO criteria, there should be at least three crypts or at least two adjacent crypts that show one or more of the above features. [3] An international expert consensus panel specified that one crypt showing characteristic distorted features is sufficient to diagnose SSA/Ps.[4] SSA/Ps are associated with the serrated neoplasia pathway and are the second-most common SP. Most SSA/Ps (75–80%) are located in the proximal colon, including the cecum, ascending or transverse colon.[20]

Traditional Serrated Adenomas

TSAs are characterized by classical cytologic dysplasia and specific features such as eosinophilic cytoplasm, ectopic crypts, and penicillate nuclei.[3] TSAs are rare relative to HPs and SSA/Ps, and typically only account for 1% of SPs.[21] TSAs are usually larger, polypoid lesions located in the distal colorectum.[22]

Unclassifiable Serrated Polyps

Unfortunately, some polyps are not easily categorized into HPs, SSA/Ps, or TSAs. For instance, adenomas can show features of serration. In addition, overlapping features between HPs and SSA/Ps as well as suboptimal tissue orientation or limited sampling can lead to difficulty in interpretation. An international expert consensus panel recommends the use of the term “serrated polyp unclassified” when a precise diagnosis of SP subtype cannot be determined.[4] While some pathologists continue to use the term “mixed polyp”, this is generally considered anachronistic and confusing terminology.

Endoscopic Detection

Endoscopic detection of SSA/Ps is difficult due to their indistinct borders and flat or sessile morphology.[23] In addition, SSA/Ps tend to be located in the right colon, a location that may be harder for colonoscopists to reach and examine fully.[8, 24] Studies from a variety of different practice settings [8, 24] have documented wide variability in SSA/P (or proximal SP) detection rates, attributable to factors related to the patient, procedure, and provider.[15, 25–27] Nevertheless, there is evidence that endoscopic detection of SSA/Ps is improving over time.[15, 28, 29]

Patient Factors:

The risk factors for SPs and SSA/Ps differ significantly from the risk factors associated with conventional adenomas.[18, 30] For instance, although African Americans have a higher risk of developing both CRC and conventional adenomas, there appears to be a lower risk of SPs and SSA/Ps in African Americans.[2, 31–33] Another risk factor that differs between SPs and SSA/Ps in comparison to conventional adenomas is male sex.[34] While males clearly have a higher risk of conventional adenomas compared to females, the same is not true for SPs and SSA/Ps; females are at equal or slightly higher risk of harboring these lesions.[21] SSA/Ps are also associated with personal history of SSA/Ps but have no apparent correlation with personal history of conventional adenomas.[35, 36]

Other risk factors for SPs are similar to conventional adenomas, such as age, tobacco and alcohol use, diabetes, and obesity. Older age appears to have a positive correlation with an increased development of SPs, though the relationship to age is less clear with SSA/Ps.[31, 35, 37] Both tobacco and alcohol use are also associated with the development of SPs and SSA/Ps.[38, 31, 33, 39] Diabetes has been shown to be a risk factor for SSA/Ps in some studies.[37] Likewise, obesity appears to be directly related to an increased numbers of SPs, [38, 33, 31] but evidence is inconclusive regarding whether obese patients have a higher risk of SSA/Ps specifically.[37, 31, 39] Smoking and a personal history of SSA/Ps are of particular interest, as multiple studies have found that patients with these risk factors who present for screening or surveillance colonoscopy have substantially higher risks of harboring SSA/Ps.[37, 35, 40]

Endoscopists should be aware of risk factors and protective factors for SPs and SSA/Ps, and have a high index of suspicion for SSA/Ps when performing colonoscopies on patients with multiple risk factors for SPs.

Procedure Factors:

Bowel Preparation—Because SSA/Ps are subtle lesions that can be difficult to detect, it stands to reason that achieving adequate bowel preparation is important to optimize SSA/P detection. Several studies have examined the importance of bowel preparation for detecting SPs, and most show either a trend[41, 27, 42] or significant association[43] between better bowel preparation and improved detection of SSA/Ps, right sided polyps, or flat lesions. Importantly, a recent prospective study with 749 patients by Clark et al. reported that any bowel preparation below adequate (Boston Bowel Preparation Score <7) resulted in a

decrease in the detection of SSA/Ps.[43] Above this threshold, the benefit of excellent preps vs. good preps is uncertain; a recent cross-sectional study determined no significant difference in SP detection rates among patients with adequate preps (BBPS score ≥ 6).[44] Nevertheless, these studies suggest that achieving adequate bowel preparation is key to enhance SSA/P detection. Additionally, there is strong evidence that split bowel preparation technique improves polyp detection, particularly in the right colon where SSA/Ps predominate.[45, 46]

Withdrawal Time—Most studies examining the association of withdrawal time and SP detection have concluded that longer withdrawal times improve SP detection rates.[27, 47] In particular, in a study of nearly 8,000 colonoscopies, Butterly et al. showed that longer withdrawal time was associated with improved detection of “clinically significant serrated polyps” (SSA/Ps or proximal HPs) with significant improvements noted for every minute above 6 minutes of withdrawal time up to a maximum of 9 minutes.[47] Importantly, this 9 minute threshold is longer than the minimum withdrawal time recommended for optimal detection of conventional adenomas (≥ 6 minutes[48, 49]), and thus further lengthening of withdrawal time (accompanied by detailed inspection) may represent an opportunity to improve SSA/P detection, particularly for endoscopists with suboptimal detection rates.

Chromoendoscopy—Chromoendoscopy involves the use of a contrast dye solution that is sprayed or irrigated upon the colonic mucosa to facilitate detection, inspection and characterization, and complete resection of mucosal lesions. This technique has shown promise in the detection of SPs.[50] A two-center German randomized controlled trial showed that chromoendoscopy significantly improved the detection rate of serrated lesions compared to conventional colonoscopy (1.19 vs 0.49 per patient, $p < 0.001$).[17] In this study, the pan-colonic chromoendoscopy colonoscopy group received a low volume indigo carmine spraying technique during withdrawal. The study also dictated a minimum of 8 minutes of withdrawal time for both groups, which could increase procedure time.[17] There remains little data from the United States on chromoendoscopy, but based on available data, chromoendoscopy appears to be a promising technique to assist with visualizing SPs.

Water Immersion—Water infusion is an alternative to air insufflation during colonoscopy. Water infusion involves filling the lumen with water, which magnifies mucosal surface features. Water immersion colonoscopy has already been shown to be helpful with adenoma detection rates and decreased procedure-related abdominal pain.[51] A few studies examine the effect of water infusion on SP detection. Leung et al. 2011 described two RCTs done in Veteran’s Affairs (VA) hospitals that showed improved detection of HPs in the proximal colon.[52] A retrospective observational study done at the VA showed that water-exchange combined with cap-assisted techniques demonstrated significantly improved detection of proximal SPs.[53] SSA/Ps were not distinguished from HPs in these studies.[52, 53] The water immersion technique can also facilitate polypectomy resection (see below).[54]

Wide Angle and Cap-assisted Colonoscopy—A variety of different techniques are available for increasing the field of view during colonoscopy to enhance mucosal inspection. Full-spectrum endoscopy (FUSE) increases the field of view to 330° compared to 170° for

conventional colonoscopy. A recent study by Hassan et al. showed that there was no significant difference in SSA/P detection rate with the use of FUSE compared to the standard forwarding viewing colonoscopy.[55] Cap-assisted colonoscopy is another technique thought to assist in visualization of areas behind colonic folds to improve detection of SSA/Ps and increase angles of visualization. Post-hoc analysis of a RCT suggested that cap-assisted colonoscopy offered a significantly higher SP detection rate of 12.8% vs. 6.6% ($p=0.047$) compared to standard colonoscopy.[56] Another type of cap is the Endocuff, an endoscopic cap with projections. In a VA retrospective study, colonoscopy assisted by Endocuff resulted in a significant increase in the SSA/P detection rate vs. standard colonoscopy (15% versus 3%).[57] In contrast, a randomized controlled trial by Van Doorn et al. showed that there were no significant differences in SP detection per patient using the Endocuff.[58] Thus the value of wide angle and cap-assisted colonoscopy for SSA/P detection is inconclusive at this point and requires further study.

Narrow Band Imaging—Narrow band imaging (NBI) is a technique that uses narrow wavelength light source to optimize the visualization of hemoglobin, seen as microvessels in the mucosa. The image enhancement allows for the distinction of colonic lesions into different subtypes, aiding in the detection of SPs. Hewett et al. described the NBI International Colorectal Endoscopic (NICE) classification that can differentiate SPs from adenomas by their lighter color, limited vessels, and homogenous spots or lack of pattern.[59] The NICE classification system resulted in 92% accuracy in differentiating SPs and conventional adenomas for gastroenterology fellows.[59] However, the NICE classification does not distinguish between HPs and SSA/Ps (both are NICE type 1 lesions), which is a significant limitation. Accordingly, the NICE classification system was later adapted into a modified classification model called Workgroup serrated polypS and Polyposis (WASP).[60] Notably, WASP features (particularly the presence of clouded surface, indistinct borders, irregular shape, and/or dark spots within crypts) help distinguish SSA/Ps from HPs. The use of WASP criteria in NBI showed improved endoscopic diagnosis of SSA/P with 79% accuracy after training.[60] NBI also has value in determining whether SSA/Ps may have foci of dysplasia.[61]

However, the benefit of NBI has mostly been demonstrated for visual diagnosis, not for detection of polyps, and whether or not use of NBI results in overall better detection rates compared to standard colonoscopy remains to be seen. In a randomized controlled trial of 800 patients at two academic medical centers, use of NBI did not significantly increase the detection rate of proximal SPs overall (0.51 vs. 0.39 lesions per patient, $p = 0.085$), but did significantly increase detection of larger proximal SPs (For proximal SP >5mm: 0.24 vs. 0.15 lesions per patient, $p = 0.027$; for proximal SP 10 mm: 0.10 vs. 0.05 lesions per patient, $p = 0.049$).[62] Another randomized crossover study of the use of NBI in patients with serrated polyposis undergoing surveillance colonoscopy found that use of NBI was associated with a lower polyp miss rate compared to standard white light endoscopy (20% vs. 29%), but this was not statistically significant ($p=0.065$). On the basis of these studies, we can conclude that NBI certainly has value for the endoscopic visual diagnosis of SPs and SSA/Ps. NBI also shows promise for use to improve the detection of SSA/Ps, but further research is needed to clarify the benefit of this technique in the screening setting.

Provider Factors:

Numerous studies demonstrate that there is a significant difference in the SP detection rate depending on the individual endoscopist.[25, 26, 63, 15] Differences in detection are likely due to a combination of provider familiarity with the characteristics of SSA/Ps, the subtle endoscopic features of these polyps, and the technical challenges of detecting and removing lesions in the proximal colon. While the literature is relatively sparse with respect to studies of provider factors associated with SP detection, a recent multicenter study of colonoscopy quality found that endoscopists who had specialty training in gastroenterology, were closer to completion of training, and those with higher procedure volumes had higher SP detection rates compared to endoscopists without these characteristics.[64]

Adenoma detection rate (ADR) is the most widely used colonoscopy quality measure, yet ADR does not necessarily capture detection of SSA/Ps. Furthermore, while ADR is correlated with SSA/P detection,[27, 25, 15] these are different metrics, and the skills needed for colonoscopists to identify SSA/Ps are not necessarily the same as those used to identify conventional adenomas.[65, 29] Various metrics have been proposed for SP detection, including 'proximal serrated polyp' (PSP) detection rate, SSA/P detection rate, and "clinically relevant SP" detection rate (which typically includes all SSA/Ps, TSAs, and PSPs). The latter two of these metrics are more important, but are also more difficult to measure due to greater reliance on accurate pathologic diagnosis (which can be variable). One retrospective single-center study observed that PSP detection rate and clinically relevant SP detection rates were highly correlated, which may mean that PSP detection rate is an adequate surrogate marker.[65] While various threshold values have been proposed, a recent analysis from Anderson et al. suggested benchmarks for SP detection of 7% for clinically significant SPs and 11% for all proximal SPs.[66]

Non-Endoscopic Detection Methods

Non-endoscopic CRC screening tests include stool tests, flexible sigmoidoscopy, capsule endoscopy, and CT colonography. These less invasive tests may also detect SPs; however, these strategies are generally considered inferior to colonoscopy.[67, 18]

Stool Tests

Stool markers including fecal occult blood testing (FOBT) and fecal immunohistochemical testing (FIT) are important screening tests for CRC but have poor detection rates for SSA/Ps in particular.[68] Fecal DNA testing is a promising technique to non-invasively detect SSA/Ps. A recently developed FIT + multitarget stool DNA test (Cologuard, Exact Sciences) contains 4 stool DNA markers: methylated BMP3, mutant KRAS, beta-actin, and methylated NDRG4. In a large multicenter validation study, this test demonstrated a sensitivity of 42% for large SSA/Ps compared to 5% with FIT alone.[69] Importantly, the detection of SSA/Ps appeared to be attributable to the methylated panel markers, which is congruent with the importance of CIMP in the serrated pathway. Other studies have also corroborated the utility of multitarget stool testing in SP detection.[70, 71] In a high risk Alaskan Native population, Redwood et al. reported an SSA/P detection rate by multitarget stool DNA test of 67% compared to an 11% rate with FIT alone.[72] Given these findings,

multitarget stool DNA testing could represent a complementary method to detect SSA/Ps in some patients, and certainly appears superior to other stool tests that rely on hemoglobin alone.

Flexible Sigmoidoscopy

Although flexible sigmoidoscopy has been shown to reduce the incidence and mortality of distal CRC, understandably, these benefits were not seen in the detection of proximal colon cancers.[73] Since higher risk SSA/Ps are predominantly located within the proximal colon, flexible sigmoidoscopy is likely insufficient for detecting premalignant SPs. Kahi et al. demonstrated that findings in the distal colorectum do not correlate with advanced proximal SPs.[74] Also of note, since sigmoidoscopy may be paired with FIT for improved detection of proximal adenomas and cancers, this strategy is also likely inadequate for detecting serrated precursor lesions because of the poor sensitivity of FOBT and FIT for these polyps. While there is strong evidence of the effectiveness of flexible sigmoidoscopy for CRC screening[75–77] and it continues to be a recommended test,[76] this is an important limitation.

CT Colonography

CT colonography (CTC) is still being explored as an alternative CRC screening test. However, CTC is generally inferior to colonoscopy with respect to polyp detection, especially for flat and sessile lesions such as SSA/Ps. A recent large scale multicenter randomized controlled trial with 8844 patients determined that colonoscopy was superior to CT colonography in the detection rate of all types of SPs, and CTC was particularly poor for the most advanced polyps.[78] The detection rate for high risk SSA/Ps was 0.8% for CT colonography compared to 4.3% for colonoscopy ($p < 0.001$).[78] There remains a debate as to whether improved CT colonography techniques such as improved contrast coating may lead to higher rates of SP detection,[79] but it is doubtful that this modality will approach the detection capabilities of colonoscopy given its reliance on polyp topography and size.

Capsule Colonoscopy

Recent studies suggest capsule colonoscopy as a reasonable method for detecting conventional adenomas in patients who had incomplete colonoscopies or who cannot undergo colonoscopies, but SSA/Ps are still incompletely characterized by capsule endoscopy.[80, 81] A multi-center prospective study of 884 patients performed at 14 centers in the US and Israel showed that the sensitivity and specificity of detecting SSA/Ps with capsule colonoscopy was particularly poor compared to adenomas and HPs.[81] Recruited patients initially received a capsule colonoscopy, followed by conventional colonoscopy several weeks later performed by an endoscopist who was blinded to the initial capsule colonoscopy results. The sensitivity for SSA/P detection was 29% (CI 10–56%) for polyps ≥ 6 mm and 33% (CI 10–65%) for polyps ≥ 10 mm in capsule colonoscopy compared to 74% (CI 62–84%) for polyps ≥ 6 mm and 81% (58–95%) for polyps ≥ 10 mm in conventional colonoscopy.[81] Based on this study, it appears that capsule colonoscopy is also inferior to conventional colonoscopy for SSA/P detection, though this modality is capable of detecting some SPs.

Resection

It is generally recommended that all SPs encountered during colonoscopy be completely removed, except for lesions ≤ 5 mm in the sigmoid or rectum.[4] Because SSA/Ps are sessile or flat, they can be challenging to remove with standard polypectomy technique and equipment. For this reason, The British Gastroenterology Society (BGS) recommends that resection of proximal SSA/Ps ≥ 10 mm in size be done by endoscopists who have demonstrated a certain level of skill at polyp resection.[67] However, it should be noted that there is some debate as to whether or not the benefits of SSA/P resection outweigh the harms of polyp removal.[82]

Types of Resection

Small suspected SSA/Ps should generally be removed using a standard cold snare polypectomy. However, the same technique cannot always be applied to large SPs due to their size. Piecemeal resection is an option for large SPs and necessitates a follow up colonoscopy in 3–6 months to assess for residual neoplasia.[67] In a two center retrospective study of 251 large SSA/Ps (≥ 10 mm), standard endoscopic mucosal resection with submucosal saline injection and subsequent stiff electrocautery snare was found to be both highly effective and safe, with low rates of local recurrence ($<4\%$) and no serious complications.[83]

Endoscopic mucosal resection can also be aided by water immersion. Intraluminal water helps separate the mucosa and submucosa from the muscularis propria and eliminates the need for submucosal injection to facilitate endoscopic mucosal resection. This has been tested as a safe and effective technique for SP resection in prospective observational studies (Figure 1).[54, 84, 85] In twenty-two patients, Binmoeller et al. resected 15 SSA/Ps at the appendiceal orifice to prove the effectiveness of the technique.[85] Curcio et al. demonstrated that SPs could be resected underwater without specific training.[84] Another method that may be useful, particularly for small flat SPs that are difficult to grip with a polypectomy snare, is the “suction pseudopolyp technique” in which suction is used to create a mucosal protuberance in order to facilitate snaring.[86] Lastly, an emerging technique for removal of large SSA/Ps in particular is piecemeal cold snare polypectomy (Figure 2). Success of this technique has been demonstrated both with [87, 88] and without submucosal injectate[89], and offers the benefit of avoiding thermal injury and reducing or eliminating the risk of late post-polypectomy bleeding. Further studies are needed to evaluate the utility, safety, and outcomes of this promising technique.

The vast majority of precancerous SPs are amenable to endoscopic resection.[90] However, in rare circumstances surgical resection may be indicated based on patient preferences and/or certain polyp features (e.g. difficult location, very large size, multiplicity).[4]

Risk of Incomplete Resection

SPs tend to have a higher likelihood of incomplete resection, likely due to their indefinite borders and inconspicuous surface features. In a prospective study by Pohl et al. involving 346 colonoscopic polypectomies (and 42 SSA/Ps), the rate of incomplete resection was 31%

for SSA/Ps compared to 7% for conventional adenomas.[91] In the same study, 48% of large polyps 10–20 mm were incompletely removed.[91] Bouwens et al. performed a retrospective series of eighteen patients that had at least one large proximal SP that was only biopsied and not resected during colonoscopy. Three out of those eighteen patients developed CRC in the proximal colon.[92] These studies suggest that the rate of incomplete resection of SSA/Ps may be substantial, and incomplete removal may be associated with interval cancer after colonoscopy.

Handling of Pathologic Specimens

In most centers, pathologic polyp specimens are directly placed into a formalin solution following polypectomy and retrieval. This sometimes results in the loss of histologic orientation after paraffin embedding and sectioning, and misidentification of SSA/Ps in particular. There is evidence that standard polyp handling techniques are not ideal for the histologic interpretation of SPs because loss of orientation can make it difficult to identify and assess the base of the crypts (Figure 3).[93] A study by Morales et al. suggests that a modified protocol in which the SPs are flattened and enclosed in a paper envelope before being placed in formalin leads to improved histopathologic interpretation and increased diagnosis of SSA/P.[94] In their study, there was improved inter-pathologic agreement with the modified protocol (77% vs. 63%, $p=0.015$) and an increased frequency of SSA/P diagnoses in the modified group compared to the conventional group (76% vs 42%, $p<0.0001$).[94]

Pathology Interpretation

SPs are characterized by a serrated appearance of the crypt epithelium. The difference between HPs and SSA/Ps lies in the degree of crypt distortion, particularly at the crypt bases. This subtle difference often results in difficulty with pathologic interpretation. As described earlier, the difference in SP subtype makes a considerable difference when clinically interpreting pathologic specimens since SSA/P and TSAs are considered pre-cancerous lesions, whereas HPs are considered more benign, and even harmless (in the case of diminutive rectosigmoid HPs). Additionally, the evolution in diagnostic criteria and nomenclature has also contributed to significant inter-rater variability among pathologists. [26, 95] In a recent study by Kolb et al., use of standard pathology criteria and a protocol to facilitate proper orientation of specimens was associated with improved interobserver agreement of SP diagnosis between pathologists.[93]

Recommended Surveillance Intervals

Colonoscopic surveillance is generally recommended for patients with SSA/Ps or TSAs in large part because of studies showing that these lesions are associated with an increased risk of future neoplasia.[96–98] SSA/Ps are also thought to give rise to a significant proportion of “interval” or post-colonoscopy CRC cases,[99] which argues for close surveillance of patients diagnosed with these polyps.

As indicated in Table 2, major groups differ slightly on their recommended surveillance intervals specific for SPs.[4, 67, 100] These guidelines are generally for colonoscopy surveillance intervals after initial screening and polypectomy, based on individuals with baseline average risk. Comparing the guideline recommended surveillance intervals, the international consensus panel guidelines are the most detailed and conservative. Whereas the British Society of Gastroenterology (BSG) and United States Multi-Society Task Force (MSTF) do not differentiate between different types of HPs, the international consensus panel differentiates HPs into higher risk if there is an increased number, larger size, or proximal location.[4, 100] Likewise, the international consensus panel also recommends shorter surveillance intervals for SSA/Ps and serrated polyposis syndrome in comparison to the BSG.[67, 4] In comparison to the MSTF, the international consensus panel recommends shorter surveillance intervals for higher risk SPs such as those with 3 SSA/Ps and SSA/P with dysplasia. [100, 4]

There is a clear need for further population analysis of SPs, as both the MSTF and BSG state that their evidence regarding SPs is “weak and low quality.” [100, 67] Areas of uncertainty are also noted in surveillance interval recommendations. Notably, there is a lack of consensus recommendations on how to manage patients with unclassifiable SPs or those with both conventional adenomas and SPs.

Prevention

There are few published studies that directly examine the question of SP prevention, but there are observational data that address this question. In 2017, Bailie et. al conducted a meta-analysis of studies examining risk factors for SPs and SSA/Ps specifically. The authors identified several different lifestyle factors that were associated with SSA/Ps in their meta-analysis including tobacco smoking (RR = 3.40) and alcohol intake (RR = 1.85). Diets high red meat and fat were found to significantly increase the risk of SPs overall [39], and one study found that high fat diets were associated with advanced SPs specifically.[33] Conversely, the regular use of non-steroidal anti-inflammatory drugs (RR = 0.62) was associated with decreased risk of SSA/Ps.[39] No significant association was found between SSA/Ps and body mass index or exercise.[39]

There is no clear role for micronutrients in the prevention of SPs. Some observational studies have linked higher intakes of calcium with reduced risk of SPs.[38, 101] However, a recent analysis from a large multicenter adenoma chemoprevention trial found that calcium supplementation (with and without vitamin D) was associated with an increased risk of SSA/Ps –6–10 years after supplementation began.[102] Additionally, supplemental folate intake appears to be associated with an increased risk of developing SPs within the right colon.[33]

Notably, two studies have analyzed the effects of hormone replacement therapy on SP formation. Burnett-Hartman et al. and Morimoto both demonstrated that hormone replacement therapy (particularly estrogen only regimens) has an inverse relationship with the development of SPs.[103, 31] However, hormone replacement therapy has other risks, and thus may not be suitable for this purpose.

In sum, there are modifiable lifestyle factors associated with SSA/Ps and SPs in general including tobacco, alcohol, and diets high in fat and red meat that represent potential targets for prevention of SSA/Ps. In addition, NSAIDs and aspirin appear to be protective factors, and thus patients with a personal history of SSA/Ps may consider using these agents, particularly if they have other risk factors for CRC.

Serrated Polyposis Syndrome

Serrated polyposis syndrome (SPS), formerly known as hyperplastic polyposis syndrome, is characterized by one of the following WHO-defined criteria: (A) five or more SPs proximal to the sigmoid colon, with two of the polyps being > 10mm; (B) >20 SPs throughout the colon (i.e. not isolated in the rectum); or (C) Any proximal SPs in an individual with a 1st degree relative with SPS.[3]

Numerous reports have shown the development of CRC in patients with documented SPS. [104–110] The estimated prevalence of SPS ranges from 1:3,000 to 1:100,000.[111–117] The median age of diagnosis of SPS is 44–62 years, with an equal prevalence of men and women.[118–120, 4] Northern European descent has been shown to increase the risk of SPS. [121] Although uncommonly diagnosed, SPS carries a 25–40% risk of CRC via the serrated pathway.[121] The accurate detection and diagnosis of SPS is important for furthering education and knowledge of this rare syndrome. However, meeting Part (C) of the criteria listed above is difficult given the under-diagnosis of SPS.

The genetic determinant(s) of SPS has not been identified. Both autosomal dominant and recessive modes of inheritance have been suggested.[112, 117, 113, 114] There appears to be an increased risk in first-degree relatives (FDR) of individuals with SPS, as Boparai et. al[122] demonstrated a relative risk of CRC in FDRs compared to the general population of 5.4 (95% CI 3.7 – 7.8). Given that there is an increased risk of CRC in individuals with SPS, increased endoscopic surveillance is necessary. The United States Multi-Society Task Force and the International Serrated Expert Consensus Panel both recommend annual colonoscopies in individuals diagnosed with SPS.[100, 4] Similar to the MSTF, the BSG recommends surveillance colonoscopies 1–2 years after diagnosing SPS.[67]

Conclusion

SSA/Ps account for about 5–10% of lesions discovered during routine screening colonoscopy. These lesions are susceptible to being missed, or (if detected) misclassified due to the difficulty in their detection, resection, and interpretation. The last two decades have brought significant advances in the understanding of the clinical significance of SPs as distinct entities from conventional adenomas, deserving of specific focus. Importantly, SSA/Ps are precursors of approximately one quarter of sporadic CRCs. Thus optimizing their detection, resection, and surveillance should be a high priority. Colonoscopy still remains the gold standard for detecting SPs. Non-endoscopic techniques such as stool testing, flexible sigmoidoscopy, CT colonography, and capsule colonoscopy are largely inadequate substitutes for colonoscopy in terms of SP and SSA/P detection rates.

Detection of SSA/Ps during colonoscopy requires a diligent endoscopist, a high quality exam, and a well trained pathologist. Risk factors for developing SPs do differ somewhat from those for conventional adenomas, which may help identify patients at higher risk for harboring these lesions. Options for optimizing detection of SPs during colonoscopy include ensuring adequate bowel preparation and increasing withdrawal inspection time to at least nine minutes, with particular attention to the proximal colon.

Once a possible SSA/P is encountered, attention to proper orientation during pathologic specimen handling can improve pathology diagnosis. Adjunctive endoscopy techniques such as chromoendoscopy, water immersion colonoscopy, wide-angle technology, and NBI demonstrate potential in helping with SP detection but need additional studies to establish their efficacy. Instituting benchmark SP detection rates (e.g. 5% for SSA/Ps and/or 10% for proximal SPs) may also help identify lower performing endoscopists (and pathologists) who need dedicated training in the recognition and diagnosis of SSA/Ps.

Once SPs are identified, published guidelines vary slightly in their recommendations, but removal of all SPs proximal to the sigmoid colon is generally recommended by US groups. Endoscopic resection of large SSA/Ps in particular can be challenging and often requires endoscopic mucosal resection and piecemeal removal with close follow up to ensure complete resection. SPs are more likely to have incomplete resections due to their flat or sessile morphology and indistinct borders. For these reasons SSA/Ps are likely responsible for a significant proportion of interval CRC. Recommended surveillance intervals for SSA/Ps largely mirror those for conventional adenomas, as serrated lesions likely have a similar (if not greater) risk of associated neoplasia. Patients with SSA/Ps may be able to lower their risk by targeting modifiable risk factors including tobacco and alcohol use, high fat diets. NSAIDs and aspirin also appear to be protective agents.

The management of SPs is a rapidly advancing field. In this review, we have provided evidence-based strategies for improving the endoscopic detection, resection, and interpretation of SPs with a particular focus on SSA/Ps due to their clinical importance. Attention to serrated class lesions is important to ensure high quality colonoscopy and optimum prevention of CRC.

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Figure 1:

Endoscopic images of a 10mm SSA/P located at the appendiceal orifice, resected en bloc with underwater endoscopic mucosal resection. A) View of water submerged SSA/P with arrows showing borders of lesion, B) Snare encircling lesion, which “floats” underwater despite not using submucosal injection, and C) Water submerged view of polypectomy site following resection. Image reprinted with permission, from Binmoeller et al. *Gastrointest Endosc* 2016

Figure 2:

Endoscopic images from piecemeal cold snare polypectomy of 2 cm sessile serrated adenoma/polyp in the transverse colon. (A) Image of SSA/P with mucus cap. (B) Submucosal injection performed to elevate lesion; (C) cold snare polypectomy begins at margin, including rim of normal tissue; (D) Image of polypectomy defect after resection is complete. Figure reproduced, with permission, from Tuttici et al. *Gastrointest Endosc* 2017.

Figure 3:

Tangential (A) vs. well-oriented (B) histopathologic sections from a sessile serrated adenoma/polyp showing the importance of sectioning for appreciating features of colonic crypts and crypt bases. Specimen A has crypt serration, but crypt bases are not well visualized. Specimen B shows dilated crypt bases with horizontal extension, consistent with a diagnosis of SSA/P.

Table 1:

Comparison of Serrated Polyps

	SERRATED POLYP SUBTYPE		
FEATURES	HP	SSA/P	TSA
Nomenclature	<p>Hyperplastic polyp subtypes:</p> <ul style="list-style-type: none"> • Microvesicular (MVHP) • Goblet cell rich (GCHP) • Mucin poor (MPHP) 	<p>Known by multiple names including:</p> <ul style="list-style-type: none"> • Sessile serrated polyp (SSP) • Sessile serrated adenoma (SSA) • Sessile serrated adenoma/polyp (SSA/P) • Sessile serrated lesion (SSL) 	Traditional serrated adenoma
Molecular features	<ul style="list-style-type: none"> • BRAF or KRAS mutation 	<ul style="list-style-type: none"> • BRAF mutation • CpG island methylation • +/- MLH1 promoter methylation • MSI (or MSS) 	<ul style="list-style-type: none"> • BRAF or KRAS mutation • Variable CpG island methylation • MGMT methylation • MSS carcinoma
Prevalence	<ul style="list-style-type: none"> • Common • 70–90% of SPs 	<ul style="list-style-type: none"> • Less common • 10–20% of SPs 	<ul style="list-style-type: none"> • Rare • 1% of SPs
Typical location	Distal colon	Proximal colon	Distal colon
Size	<ul style="list-style-type: none"> • Diminutive or small • Typically 5mm 	<ul style="list-style-type: none"> • Small to large • Median size 5–7mm 	<ul style="list-style-type: none"> • Typically large • Median size 12mm
Gross morphology	<ul style="list-style-type: none"> • Flat or sessile • Smooth texture 	<ul style="list-style-type: none"> • Sessile or flat • Smooth or bumpy texture • Paris Classification Is, Ila, or IIb 	<ul style="list-style-type: none"> • Pedunculated • Lobular texture • Paris Classification Ip
Endoscopic features	<ul style="list-style-type: none"> • Pale-colored • NICE type 1 • Papillary or stellate pit pattern 	<ul style="list-style-type: none"> • Pale-colored • Mucus cap • Rim of debris or bubbles • Cloud-like surface 	<ul style="list-style-type: none"> • Reddish color • Glandular appearance • Combined stellate and/or tubular pit pattern

	SERRATED POLYP SUBTYPE		
		<ul style="list-style-type: none"> • Alteration of mucosal fold contour • Indistinct borders • Interruption of underlying mucosal vascular pattern • NICE type 1 • Open pit pattern 	
Histology	<ul style="list-style-type: none"> • Straight crypts that rise perpendicularly from the muscularis mucosa to the polyp surface • Minimal cytological atypia 	<ul style="list-style-type: none"> • Deep crypt serration • Crypt dilation • Branched crypts • Abnormally shaped crypt bases such as L or inverted T shapes • Irregular distribution of crypts 	<ul style="list-style-type: none"> • Ectopic crypts • Eosinophilic cytoplasm • Pencillate nuclei
Dysplastic Potential	<ul style="list-style-type: none"> • Low/no dysplastic potential 	<ul style="list-style-type: none"> • Moderate dysplastic potential • 14–18% dysplastic 	<ul style="list-style-type: none"> • High dysplastic potential

Abbreviations: MSI, microsatellite instable, MSS, microsatellite stable, NICE: Narrow band imaging International Colorectal Endoscopic classification

Table 2:

Published Recommended Surveillance Intervals of Serrated Polyps

Index colonoscopy findings	International Consensus Panel ⁴	United States Multi-Society Task Force ⁹⁹	British Society of Gastroenterology ⁶⁶
HP <10 mm, rectosigmoid	10 years	10 years	10 years
3 HP, 5 mm, proximal	10 years	N/A	10 years
4 HP, proximal	5 years	N/A	10 years
1 HP, >5 mm	5 years	N/A	10 years
1–2 SSA/P or TSA, <10 mm	5 years	5 years	10 years
1 SSA/P or TSA, 10 mm	3 years	3 years	3 years
3 SSA/P or TSA, <10 mm	3 years	5 years	10 years
2 SSA/P, 10 mm	1–3 years	3 years	3 years
SSA/P with Dysplasia	1–3 years	3 years	3 years
Serrated Polyposis Syndrome ^a	1 year	1 year	1–2 years

^aPatients with (1) 5 SPs proximal to the sigmoid with 2 10 mm, (2) any SPs proximal to sigmoid with family history of serrated polyposis syndrome; or (3) >20 SPs