Serrated Polyps and Serrated Polyposis Syndrome

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Abstract

Keywords

- ▶ serrated polyps
- ▶ sessile serrated adenoma/polyp
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Colorectal serrated polyps are intermediate lesions in the serrated neoplastic pathway, which account for up to 30% of colorectal cancers. This pathway is biologically distinct from the adenoma-to-carcinoma sequence, with associated cancers exhibiting mutations in the *BRAF* oncogene, DNA promoter hypermethylation, and microsatellite instability. An evolving understanding of these unique lesions has led to the development of a more accurate classification, improved endoscopic identification, and tailored clinical management guidelines. This article reviews serrated polyps and serrated polyposis syndrome.

Colorectal cancer (CRC) develops from a series of genetic and epigenetic changes starting in the colorectal mucosa with progression through intermediate premalignant polyps. Historical concept was that all CRCs arose from conventional adenomas via inactivation of a key tumor suppressor gene, *APC*, and resultant chromosomal instability (CIN)¹ or loss of heterozygosity (LOH), as discussed in the article “Polyp Genetics” by Drs Klos and Dharmarajan, on pp. 289–295. Support for parallel pathways of carcinogenesis now exists (as previously discussed, distinct from the conventional adenoma-to-carcinoma sequence), some of which are characterized by DNA hypermethylation and microsatellite instability (MSI) with serrated polyps as the precursor lesion.² Serrated lesions are a heterogeneous group with various premalignant potential ranging from benign to dysplastic. Although previously unrecognized as premalignant, recent evidence implicates colorectal serrated lesions as responsible for nearly 30% of CRC, and an even higher percentage of interval CRCs.² As the genetic and molecular pathways of CRC carcinogenesis continue to be unraveled, the serrated pathway to neoplasia proves to be an equally critical component.

History, Definition of Terms, and Histologic Diagnosis

Our understanding of serrated polyps has evolved over the last three decades. Historically, colorectal polyps were divided into two broad categories: neoplastic (adenomas) and non-neoplastic (hyperplastic and hamartomatous). These categories were histologically distinct with adenomatous polyps having dysplasia and were thus considered precancerous, whereas hyperplastic polyps (HPs) were always considered innocuous, noncancerous lesions. It is now recognized that these polyps previously given the label of “hyperplastic” are actually a diverse group of heterogeneous polyps, now termed serrated lesions. Histologically, they exhibit a saw-toothed, “serrated crypt” architecture that forms as cells at the top of the crypt forego apoptosis and start to fold back toward the base of the crypt. These polyps are now recognized as potentially precancerous with subsets that are precursors to CRC through a molecular pathway distinct to the traditional adenoma-to-carcinoma sequence.

In 1980, a group from St. Mark's Hospital, London, England, published a series of seven patients with numerous, frequently

large metaplastic (hyperplastic) polyps.³ They proposed that these “metaplastic polyposis” patients were not at increased risk of CRC, erroneously propagating conventional wisdom at the time that serrated polyps have no malignant potential.⁴ In 1983, the pathologist Jeremy Jass raised the possibility that metaplastic polyps are precancerous, but also dismissed this possibility because there was no clinical evidence.⁵ As the vast majority of serrated polyps are innocuous, left-sided HPs, one can see in hindsight how Jass and others’ analyses were overlooked. One year later, however, Urbanski et al reported a case of adenocarcinoma arising in a mixed hyperplastic-adenomatous polyp.⁶ In 1990, Longacre and Fenoglio-Preiser first attempted to systematically separate out a clinically important subcategory of serrated polyp, the “serrated adenoma,” which led to our recognition of traditional serrated adenomas (TSAs).⁷ Another piece toward solving the serrated polyp “puzzle” occurred when Torlakovic and Snover came full circle and critically analyzed a group of six hyperplastic polyposis patients. They found that many serrated polyps in these patients were unique in that they were large, right-sided, sessile, and lacked cytologic dysplasia, and they dubbed these particular lesions “sessile serrated polyps” and “sessile serrated adenomas” depending on the absence or presence of cytologic dysplasia, respectively.⁸

By the mid-1990s, the three major serrated polyp subtypes had been reported and described in the literature, but it took another decade to firmly establish the three major diagnostic categories of serrated polyps: HP, sessile serrated adenoma/

polyp (SSA/P) with or without dysplasia, and TSA,⁹ and these categories were further cemented in the diagnostic lexicon with the most recent edition of the World Health Organization (WHO) classification.¹⁰ As diagnostic criteria were being fine-tuned around the turn of the century, an explosion of molecular data was being generated on colorectal polyps and carcinomas. The incorporation of the morphologic features of serrated polyps combined with molecular phenotyping has led to our current understanding of the serrated pathology and pathway of colorectal neoplasia. All of these lesions have serrated architecture but different genetic and molecular profiles and varying potential for CRC development.

Hyperplastic Polyps

HPs are the most common serrated polyp in the large bowel, accounting for >75% of serrated lesions. They are typically small (<0.5 cm) and located in the sigmoid colon or rectum. Larger, left-sided HPs typically reveal secondary trauma/prolapse and may be misdiagnosed as SSA/P.¹¹ Three subtypes of HPs have been described: microvesicular, goblet cell-rich, and mucin-poor. Although the subtypes have demographic and molecular differences, they are not routinely reported in pathology reports. HPs are characterized by elongation of the crypts with variable degrees of serration, particularly toward the luminal aspect of the polyp (→ Fig. 1a). Importantly, the crypts are straight and simple, and the nuclei are small and regular (i.e., there is no cytologic dysplasia).

Fig. 1 Hematoxylin and eosin-stained sections of colorectal serrated polyps, which are all characterized by “sawtooth” configuration to their crypts. (a) Hyperplastic polyps (HP) are generally small, contain simple glands and lack cytologic dysplasia (original magnification $\times 72$). (b) Sessile serrated adenomas/polyps (SSA/P) are often larger than HPs and demonstrate irregular and branched crypts. Characteristically, SSA/Ps reveal serrated crypt contours all the way to the muscularis mucosae with lateral “L-shape” at the crypt bases (original magnification $\times 64$). (c) SSA/Ps may contain cytologic dysplasia (original magnification $\times 100$). (d) Traditional serrated adenomas (TSA) are the least common serrated polyp and typically reveal striking cytoplasmic eosinophilia, a tubulovillous architecture and aberrant proliferation sites, ectopic crypt foci (original magnification $\times 30$). TSA dysplasia is characteristically unique with pale-staining, pencil-like nuclei, but may also show conventional “adenoma-type” dysplasia.

Sessile Serrated Adenomas/Polyps

There has been some debate among pathologists over the nomenclature of these lesions with some championing sessile serrated adenomas while others support the term sessile serrated polyps (SSPs). Both terms are synonymous and describe the same lesions. Expert panels have adopted the terms sessile serrated adenoma/polyp (SSA/P) to avoid this confusion,¹² and this will be the convention used in this article. SSA/Ps are the second most common serrated lesion of the large bowel, making up 15 to 25% of serrated polyps. SSA/Ps are usually larger than HPs, are more commonly found proximal to the splenic flexure, and have a flat, soft appearance, often resembling edematous normal mucosa. There is a mild female predominance. Similar to HPs, most SSA/Ps lack cytologic dysplasia and demonstrate a serrated crypt architecture. In contrast to HPs, however, SSA/Ps exhibit a disorganized, distorted crypt pattern due to an asymmetrical proliferative zone. Histologically, this is manifested as “boot-shaped,” “L-shaped,” dilated, or branching at the base of the crypts (►Fig. 1b). The crypt bases contain goblet and other mucinous cells that produce excessive mucin, often filling the crypts and coating the surface of the polyp to produce a “mucous capping” appearance that assists endoscopic detection.

SSA/Ps are also subcategorized by the presence of adenomatous dysplasia and are then classified as SSA/Ps with dysplasia. This finding places these lesions further along the spectrum of malignant progression in the serrated pathway to CRC.^{10,12} Cytologic dysplasia uncommonly occurs in SSA/Ps, but when observed, it is reminiscent of dysplasia seen in conventional adenomas (►Fig. 1c). Adenomatous changes are represented by elongated cells with increased mitoses, hyperchromatic pseudostratified nuclei, and amphophilic cytoplasm.¹² Because of the existence of both serrated architecture and classic adenomatous changes, these lesions were thought to be two separate processes that independently developed next to each other. Thus, they were formerly called “mixed polyps” or “collision polyps.” The newer term of SSA/Ps with dysplasia represents the knowledge that this is a progression within the same lesion. Although difficult to precisely determine, the natural history of SSA/P seems to be that of slow growth and evolution to dysplasia. However, once dysplasia occurs, rapid progression to high-grade dysplasia and carcinoma are considered the norm. Another form of dysplasia classified as serrated dysplasia may also be seen in SSA/Ps. In contrast to adenomatous changes, serrated dysplasia demonstrates proliferation of atypical cuboidal cells with increased mitoses and enlarged, prominent round nucleoli. The significance of serrated dysplasia is still uncertain, but many believe it also represents malignant progression.

Traditional Serrated Adenomas

TSA is the least common serrated polyp in the colon and rectum. Contrary to SSA/P, TSAs tend to be left sided and small (<1 cm).¹⁰ While it took quite some time for pathologists to recognize TSAs, classic examples are quite distinctive. TSAs have a characteristic of tubulovillous architecture with bulbous or “tennis racket” villi (►Fig. 1d). In addition to serrated crypt contours, TSAs typically reveal a distinctive cytoplasmic eosinophilia as well as small, elongated, “pencilate” nuclei.

However, larger examples of TSAs often reveal conventional adenoma-type dysplasia.¹³ The most important criterion in separating TSAs from SSA/Ps is the identification of aberrant crypt foci, whereby the crypts are no longer anchored to the muscularis mucosae.¹⁴ Conventional adenomas, however, also demonstrate aberrant crypt foci, at least in a minority of cases.¹⁵ Because TSAs have an endoscopic appearance most similar to conventional adenomas, they may present less of a detection challenge endoscopically than SSA/Ps and are not as often overlooked as other subtypes.

Molecular Features of Serrated Polyps

The serrated pathway, also discussed earlier in this issue, is largely characterized by two molecular alterations: *BRAF* V600E mutations and high CpG island methylation phenotype (CIMP-H). *BRAF* mutations are an early and defining event in the vast majority of microvesicular HPs and SSA/Ps. Neoplastic progression occurs via promoter methylation and inactivation of key tumor suppressor genes and the mismatch repair gene, *MLH1*. *MLH1* promoter hypermethylation and loss of expression is a key event in the transition of SSA/Ps with high-grade dysplasia to invasive carcinoma (sporadic MSI-H).^{16–18} The molecular features of TSA are less well understood, but *KRAS* mutations and CIMP-H are often important events. Interestingly, only approximately one-third of CRCs arising in serrated polyposis patients harbor *BRAF* mutations, implying that the majority of carcinomas develop outside of the serrated pathway in serrated polyposis patients.¹⁹

Epidemiology

Contemporary epidemiology of serrated lesions is based on studies that predate modern understanding of serrated neoplasia and are limiting in several ways. Early studies published observations of HPs, which likely included all subgroups of serrated lesions, as they are known today, without discriminating between subtypes. Furthermore, seemingly innocuous polyps were historically ignored and not removed or documented by endoscopists, thereby likely underestimating their prevalence. Only recently investigators have examined the characteristics of individual subtypes and their epidemiologic impact. Early autopsy studies suggest that 25 to 40% of Caucasian adults have at least one serrated lesion (including HPs), although great variability exists.^{20,21} In average-risk screening populations, the reported prevalence of SSA/Ps is 2 to 7%, depending on modality of identification.^{22,23} Studies evaluating use of chromoendoscopy in this population have shown a prevalence of up to 14%.^{24,25} Prevalence increases only slightly with age, compared with a dramatic increase in prevalence of adenomas with age. Gender association is also variable, with some studies supporting a higher incidence in men and others reporting that women comprise nearly 60% of those exhibiting SSA/Ps.²²

Because most serrated lesions are distally located, small HPs, knowledge regarding risk factors for development of serrated lesions is predominately based on characteristics of

this subtype. Cigarette use has been associated with development of both distal and proximal serrated lesions, although its association with distal lesions is more strongly supported in the literature.^{26–28} Fiber and calcium intake, alcohol use, and nonsteroidal anti-inflammatory drug use have been correlated with distal serrated lesions in some studies.^{29,30}

There is little report about risk factors specific for SSA/Ps. Several studies have identified cigarette smoking as a risk factor for these polyps. The role of obesity and gender are less clear, although a correlation with female gender is favored.^{31,32}

Serrated Polyps as Intermediary Lesions in the Serrated Pathway to Colorectal Cancer

Polyps and the Genetic Changes Associated with Progression

Although CRC has a genetic and molecular heterogeneity that is still being delineated, it is known that CRC develops through at least three major molecular mechanisms, as discussed earlier in this issue. To review, most CRCs arise as a result of CIN or LOH via the classical adenoma-to-carcinoma sequence with the conventional adenoma as a precursor lesion.¹ Less commonly, CRC develops via a pathway characterized by defective DNA mismatch repair (MMR) mechanisms, either by way of heritable germline mutations (15%) or sporadic MMR deficiency due to epigenetic events (85%). These sporadic unrepaired mutations are caused by loss of MLH1 function due to hypermethylation of the gene promoter region, which silences its transcription. Loss of MMR function results in an MSI-H CRC.²

Methylation of DNA is a normal molecular process used to regulate gene expression. In general, increased methylation of the promoter region reduces gene expression, and less methylation allows for increased gene expression. When overt methylation, or hypermethylation, occurs in a promoter region of a tumor suppressor gene, the stage is set for carcinogenesis. As this process does not alter DNA sequencing directly, it is considered an “epigenetic” rather than a genetic event. DNA hypermethylation tends to occur in cytosine and guanine-rich promoter regions, otherwise known as CpG islands, and the neoplasms that subsequently develop are described as CpG island methylator phenotype (CIMP)-associated tumors.

Serrated lesions are the precursor lesions in this epigenetic (hypermethylator) pathway. Although the understanding of these events is still evolving, it is believed that a *BRAF* mutation is the initiating step that allows transformation of normal mucosa to a microvesicular HP. DNA hypermethylation further drives loss of key gene transcription and progression to an SSA/P. DNA hypermethylation in the *MLH1* promoter region silences MMR gene protein translation which eventually yields an MSI-H CRC (►Fig. 2).

Evidence of Malignant Progression

Malignant potential of SSA/Ps as a marker for CRC is supported by both molecular and histologic evidence. SSA/Ps have been associated with the presence of synchronous MSI-H CRCs, and also with the presence of other serrated polyps.^{33,34} Serrated lesions ≥ 1 cm in size are strongly associated with synchronous proximally located cancers that exhibit higher rates of CIMP,

Fig. 2 Schematic representation of the serrated oncogenic pathway to colorectal neoplasia. Normal colorectal mucosa is converted into a microvesicular polyp or a sessile serrated adenoma/polyp (SSA/P) following a *BRAF* mutation. DNA hypermethylation leads to further progression and eventually to dysplasia with increasing CpG island methylation (CIMP). The resulting colorectal cancer is a methylated cancer usually with microsatellite instability.

MSI, and *BRAF* mutations than solitary CRCs.³⁵ Goldstein et al reported that patients who underwent resection of SSA/P at a particular location subsequently developed MSI-H CRC in the same anatomic location as the initial polypectomy.³⁴ In a pathology series of 2,416 SSA/Ps, 14% exhibited dysplasia (12% low-grade dysplasia and 2% high-grade dysplasia), with 1% demonstrating CRC development. Elements of SSA/P along with dysplasia and also adenocarcinoma have been identified in the same lesion, illustrating this malignant progression that is thought to contribute, at least in part, to development of interval CRCs (►Fig. 3).³⁶ Interval CRCs are more likely to exhibit features of the serrated pathway (MSI-H, CIMP-H), and may represent missed or incompletely resected lesions, or rapid progression of new lesions.^{37,38}

Fig. 3 Malignant transformation in the serrated pathway demonstrated by the presence of cytologic high-grade dysplasia (HGD) and invasive adenocarcinoma contained within a sessile serrated adenoma/polyp (SSA/P). (hematoxylin-eosin, original magnification $\times 20$). (Reprinted with permission from JNCCN—Journal of the National Comprehensive Cancer Network. Sessile Serrated Polyps: An Important Route to Colorectal Cancer. J Natl Compr Canc Netw 2013;11:1585–1594.)⁴⁶

Endoscopic Management of Serrated Lesions

Detection

It is well accepted that colonoscopy with detection and resection of adenomas reduces mortality from CRC, but is less protective for the development of right-sided cancers.^{39,40} As many right-sided colon cancers exhibit molecular features of the serrated pathway, such as CIMP and MSI, it is suspected that SSA/Ps play an important role as precursor lesions. Ineffective identification and removal of these precursor lesions may contribute to cancer development, particularly the development of interval CRCs.

Several unique characteristics of SSA/Ps contribute to challenging endoscopic identification, reflected in the variable detection rates of serrated lesions even among experienced endoscopists.²² They typically have a flat, or sessile, morphology, with a pale, translucent appearance similar in color to adjacent mucosa.⁴¹ With taut insufflation, they often become so inconspicuous that they seem to disappear into surrounding mucosa. Their indistinct borders allow them to easily be mistaken for an ordinary contour of a fold of normal mucosa. Another unique endoscopic feature of serrated lesions is the presence of a bronze “cap” of mucus, stool, or bile, which outlines the rim of the polyp, thereby allowing for better visualization as long as this debris is not rinsed prior to identification. This is particularly helpful in identifying HPs and SSA/Ps. TSAs have an appearance more similar to classic adenomas, and are considered more easily identified (and less frequently missed) than HPs and SSA/Ps (—Fig. 4).^{12,37}

The use of endoscopic chromoendoscopy may improve serrated lesion detection. Two large, randomized studies

showed significantly improved serrated polyp detection using chromoendoscopy compared with standard white light colonoscopy, but at the cost of increased procedural time.^{24,25} The optimal clinical scenario for this technique remains undefined, but it may be a useful approach in selected high-risk patients such as those with a history of high-risk or large proximal serrated polyps, or those with serrated polyposis syndrome (SPS).

Although true prevalence studies are lacking, a serrated polyp detection rate of 15% has been suggested to ensure high-quality endoscopy. Serrated polyp detection rate is improved by longer withdrawal times and correlates with adenoma detection rates for screening exams.⁴² Endoscopists should employ meticulous inspection of the mucosa, generous withdrawal times, and recognition of the challenging endoscopic features of serrated lesions to reduce miss rates.

Polypectomy

Because of malignant progression risk and the inability to distinguish benign from malignant lesions, all polyps detected during colonoscopy should be removed.¹² An exception is the multiple diminutive (< 5 mm), typical hyperplastic-appearing lesions in the rectosigmoid. Single lesions should be removed, but when larger numbers preclude complete removal, representative lesions should be biopsied. In the past, experience with endoscopic removal of serrated lesions was minimal, as they were often left alone due to their perceived harmless nature and had an appearance distinct to adenomas. Currently, principles for endoscopic resection are similar to those for adenomas, with a few guidelines specific to the resection of these challenging lesions.

The characteristic indistinct border of serrated lesions makes complete resection difficult at times, particularly large polyps with flat morphology.⁴¹ This is especially relevant given the known association of serrated lesions to development of interval CRCs, as incomplete resection of at-risk mucosa may increase the likelihood of interval cancer development.⁴³ The use of advanced techniques such as narrow band imaging, chromoendoscopy, or high-definition colonoscopy may be helpful in discerning borders and ensuring complete resection of all polyp tissue.

Except for the most diminutive polyps, hot snaring is favored over piecemeal removal with forceps because of its efficiency in complete polyp removal including a rim of normal mucosa. The mucosa of serrated lesions tends to gather in a snare more easily than adenomas because of the loose attachment of the mucosa to the underlying submucosa. Mucosal tissue, even in smaller polyps, is drawn in easily and allows for efficient and complete removal. Submucosal injection may impede this process and is generally not necessary or recommended.⁴⁴ If the lesion is exceptionally large or the resection margins are difficult to assess, polypectomy over two colonoscopies may be needed. If the pathology is benign, it is reasonable to repeat the endoscopy in 3 to 6 months to assess the completeness of resection and to check for any residual or recurrent polyp at that time.

Serrated lesions in the right colon and cecum pose an additional challenge due to a thin colonic wall and likely flat

Fig. 4 Colonoscopic images of serrated lesions. They are often difficult to see, pale, and covered by a bronze “cap” of mucus or stool.

morphology, with a greater risk for perforation and hemorrhage. These lesions can be managed safely, but should be reserved for an experienced endoscopist. A retrospective study of 132 large (≥ 2 cm) SSA/Ps, over half located in the cecum/ascending colon, showed that safe resection was feasible in experienced hands, with a complication rate (4%) comparable to that for the removal of adenomas of similar size.⁴⁴ For further considerations of removal of colorectal polyps, see “Colonic Polyps: Treatment” by Drs Huang and Sarin (on pp. 306–314), and “Management of Rectal Polyps” by Drs Cowan and Silveira, on pp. 315–320.

Recommendations for Surveillance and Interval Colonoscopy

Postpolypectomy surveillance guidelines for serrated lesions continue to evolve as we learn more about the natural history of these lesions. Colonoscopic surveillance guidelines have traditionally been based on adenomas found at index colonoscopy, with little emphasis placed on subsequent serrated

neoplasia risk. However, recent recognition of the importance of the serrated pathway to CRC development has led to new recommendations, specifically for serrated polyps. In fact, surveillance intervals may need to be shorter than those for adenomas due to the high prevalence of CIMP-H and MSI-H interval CRCs. An expert multidisciplinary panel recognized several high-risk serrated polyp features that helped draft surveillance recommendations. This consensus statement recommends surveillance and treatment of serrated lesions *at least* as aggressively as for adenomas, and considers that the risk for developing CRC through the serrated pathway is influenced by the number, size, histologic type, and anatomic distribution of the serrated lesions (► **Table 1**).¹² It is emphasized that the success of this proposed risk stratification scheme is dependent on the combination of accurate identification and removal by a well-trained endoscopist and accurate histologic assessment by a pathologist with specific understanding of these lesions. A recent U.S. Multi-Society Task Force also recognized the importance of serrated lesions and proposed similar recommendations.⁴⁵

Table 1 Guidelines for serrated polyp surveillance

Histology	Size (mm)	Location of polyps	Number of polyps	Surveillance interval (y)
HP	<10	Rectosigmoid	Any	10
HP	≤5	Proximal to sigmoid	≤3	10
HP	Any	Proximal to sigmoid	≥4	5
HP	>5	Proximal to sigmoid	≥1	5
SSA/P or TSA	<10	Any	<3	5
SSA/P or TSA	≥10	Any	1	3
SSA/P or TSA	<10	Any	≥3	3
SSA/P	≥10	Any	≥2	1–3
SSA/P with dysplasia	Any		Any	1–3

Abbreviations: HP, hyperplastic polyp; SSA/P, sessile serrated adenomas/polyp; TSA, traditional serrated adenoma.

Source: Modified with permission from Rex et al.¹²

Indications for Surgery

The management of serrated lesions of the colorectum centers on endoscopic identification and resection. However, not all serrated polyps may effectively or safely be removed endoscopically. Colorectal surgery consultation should be considered when a CRC has been identified, if a polyp cannot be completely removed, if the polyp burden cannot be effectively managed endoscopically, or if there is rapid progression in the size or number of lesions on interval colonoscopy.⁴⁶ The extent of colon resection depends on the location of the pathology, as well as on polyp burden and distribution. Cancers and unresectable polyps with high-grade dysplasia can be adequately treated with segmental colectomy following oncologic principles. The development of metachronous left-sided colon cancer after right colectomy for a serrated pathway right-sided colon cancer is rare.⁴⁷ Patients must therefore be counseled regarding the risk for subsequent development of CRC, even when they are compliant with sequential and sometimes frequent exams. Of note, the use of minimally invasive approaches, including combined colonoscopic/laparoscopic approaches, have made surgical resection for polyps not amenable to colonoscopic resection a more patient-friendly option with less pain and quicker return to work. These approaches are addressed in “Colonic Polyps: Treatment” by Drs Huang and Sarin (on pp. 306–314).

Serrated Polyposis Syndrome

SPS, formerly called *hyperplastic polyposis syndrome*, is characterized by many or a few large colorectal serrated polyps. SPS is a clinical diagnosis, defined by WHO criteria as follows: more than 20 serrated polyps of any size, distributed throughout the colon; at least five serrated polyps proximal to the sigmoid colon with two or more larger than 10 mm; any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS.¹⁰ Any one of the criteria satisfies the diagnosis. The polyp counts are cumulative over time and all serrated lesions (HPs, SSA/Ps, and TSAs) qualify. Despite being defined by serrated polyps, adenomas are also frequently seen.⁴⁸

Although SPS is believed to have a hereditary predisposition, no genetic cause has been identified. The condition has a median age at diagnosis of 44 to 62 years and near-equal gender distribution. Risk factors for SPS are unclear, as cases may have a heritable cause or may develop secondary to environmental agents not yet recognized.

The prevalence of SPS is difficult to determine given an unknown denominator of asymptomatic unscreened individuals, and an incomplete recognition of this phenotype by endoscopists. One series estimates approximately 1 in 3,000 people have SPS based on screening colonoscopies.⁴⁹ However, these estimates are likely low, as this does not include people younger than 50 years (who do not undergo routine screening) and the general lack of familiarity with the disease or its diagnostic criteria. One recent retrospective review reported that 1.8% of patients with at least one serrated polyp met criteria for SPS.⁵⁰ We suspect that as more endoscopists become more aware and familiar with this syndrome, the reported incidence will increase.

Much like incidence, the CRC risk associated with SPS is difficult to be accurately predicted due to the unknown true denominator, ascertainment bias, and lack of good natural history studies. Estimates of CRC in SPS are reported to be approximately 25 to 40% based on larger series in the literature. The cancer risk is similar regardless of the diagnostic criteria met.⁴⁸ Importantly, patients may be diagnosed with SPS only after they have developed CRC and the polyp burden only manifests during surveillance colonoscopies.

Management of SPS is based on the goal of preventing CRC development and deaths from CRC. Thus, management is based on endoscopic control, with surgical referral when this is no longer safe or feasible. Once an SPS diagnosis is made, annual colonoscopy with polyp clearance is recommended.^{12,45} National Comprehensive Cancer Network (NCCN) guidelines recommend less frequent examinations, every 1 to 3 years depending on number and size of polyps.⁵¹ The authors recommend consultation with a colorectal surgeon who is knowledgeable of this disease at the time of diagnosis. Associated CRC risk, effectiveness of endoscopic management, and the role of surgery should be discussed with the patient.

Most patients, particularly those with large, right-sided polyps, can be managed endoscopically with polypectomy. CRC obviously mandates formal resection. Surgery should also be considered in patients whose polyp burden cannot be effectively managed endoscopically due to the polyp number, size, location, or rapidity of development or change. Patients who cannot undergo adequate colonoscopic surveillance for technical reasons, patients who do not wish to follow surveillance recommendations, or patients who have a large risk aversion and request aggressive risk reduction should also be considered for operative intervention. Given the associated cancer risk, when surgery is indicated, a total abdominal colectomy and ileorectal anastomosis should be considered in the medically fit patient, assuming the rectum is spared of pathology. This also depends on the overall polyp burden and phenotype. If the polyps or CRCs have been focal, a segmental colectomy may be considered, with the caveat that any remaining colorectal mucosa needs to be surveyed annually. These recommendations are in flux and may be better defined as more is learned about the natural history of the disease.

Even though the suspected inheritance pattern of SPS is unclear, almost half of SPS patients have a family history of CRC with one study reporting an elevated relative risk of CRC of 5.4 in first-degree relatives of patients with SPS.⁵² These data support close screening of first-degree relatives with colonoscopy recommended to begin at whichever of the following is earliest: age 40 years, at the same age of diagnosis if SPS is uncomplicated by CRC, or at an age 10 years younger than the age at diagnosis of CRC in the setting of SPS.^{12,45,51}

Conclusion

The serrated oncogenic pathway is responsible for approximately 30% of CRCs, including the clinically challenging right-sided interval cancers. Mutations in *BRAF*, abnormal CIMP, and MSI are hallmarks of this pathway, with SSA/Ps recognized as a key intermediary. Appropriate endoscopic recognition and treatment requires an understanding of the typical appearance, accurate identification, and effective and safe removal of serrated lesions. We recommend hypervigilance for these lesions and aggressive endoscopic and surgical management due to their potential rapid progression to cancer. SPS is the representative WHO-defined polyposis syndrome of the serrated cancer pathway with an increased risk of CRC development. Accordingly, these patients need regular colonoscopic surveillance to manage their cancer risk. Clinical practice guidelines now recommend surveillance strategies that better reflect our current understanding of the malignant potential of these unique lesions.

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