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Serrated Colon Polyps as Precursors to Colorectal Cancer

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Abstract

Identification of the serrated neoplasia pathway has improved our understanding of the pathogenesis of colorectal cancer (CRC). Insights have included an increased recognition of the malignant potential of different types of serrated polyps, such as sessile and traditional serrated adenomas. Sessile serrated adenomas share molecular features with colon tumors, such as microsatellite instability and a methylator phenotype, indicating that these lesions are precursors that progress via the serrated neoplasia pathway. There is evidence that the serrated pathway contributes to interval or missed cancers. These data have important implications for clinical practice and CRC prevention, since hyperplastic polyps were previously regarded as having no malignant potential. Endoscopic detection of serrated polyps is a challenge because they are often inconspicuous with indistinct margins, and are frequently covered by adherent mucus. It is important for gastroenterologists to recognize the subtle endoscopic features of serrated polyps, which would facilitate their detection and removal, to ensure a high-quality colonoscopy examination. Recognition of the role of serrated polyps in colon carcinogenesis has led to the inclusion of these lesions in post-polypectomy surveillance guidelines. However, an enhanced effort is needed to identify and completely remove serrated adenomas, with the goal of increasing the effectiveness of colonoscopy to reduce CRC incidence.

Keywords

Serrated Polyps; Sessile Serrated Adenomas; Serrated Polyposis Syndrome; Colon Cancer

I. Introduction

Colorectal carcinoma (CRC) is the most common gastrointestinal malignancy worldwide¹, and most cases originate from identifiable precursor lesions. Traditionally, epithelial polyps of the colorectum were classified as either hyperplastic or adenomatous with the adenomatous polyps representing the principal precursor to CRCs. However, advances in the

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molecular understanding of CRC suggest it is a heterogeneous disorder arising via multiple pathways including the serrated pathway, whereby the serrated polyp is the precursor lesion. In this pathway, a distinct subtype of serrated polyps [known as sessile serrated adenomas (SSA/Ps)] has become recognized as an important contributor to CRC incidence². Serrated polyps have distinct histopathological features. Their often subtle appearance at endoscopy poses challenges for endoscopic detection and removal, which are critical for CRC prevention. In this manuscript, we review the classification of serrated polyps, the molecular characteristics of the serrated neoplasia pathway, and the detection and appropriate management of these lesions.

II. Pathology of Serrated Polyps

Classification

Serrated polyps are heterogeneous lesions characterized histologically by glandular serration, i.e., a “saw-tooth” infolding of colonic crypt epithelium. This feature is believed to be the result of increased cell turnover combined with delayed migration or failure of apoptosis at the mucosal surface leading to an accumulation of epithelial cells that are accommodated by infolding (serration) of the epithelial crypt lining³. Historically, polyps with serrated architecture were considered indolent, hyperproliferative, non-neoplastic hyperplastic polyps. It is now recognized that several distinct subtypes of serrated polyps exist, and a subset may progress to invasive cancer through a serrated neoplasia pathway. Serrated polyp nomenclature is in evolution. The most recent classification by the World Health Organization (WHO) categorizes them into two main groups based on the presence or absence of dysplasia (Table 1). This includes serrated polyp subtypes: hyperplastic polyps, sessile serrated adenoma/polyp (SSA/P), SSA/P with cytological dysplasia, and traditional serrated adenoma (TSA).⁴

Hyperplastic Polyp (HP)

The defining histologic feature of HPs is a sawtooth pattern of epithelial infolding in the upper half of the crypt with a lack of cytologic dysplasia (Figure 1A). HPs are subclassified into microvesicular, goblet cell-rich, and mucin-poor variants³. The microvesicular type is most frequent type and is characterized by epithelial cells with small droplets of cytoplasmic mucin and decreased goblet cells. There is abundant serration in the upper portion of the crypt, but the crypt base is straight. The microvesicular subtype often has mutation in the *BRAF* oncogene, suggesting these could be precursors to SSA/P⁵. In contrast, goblet cell-rich HPs have abundant goblet cells, less superficial serration and lack *BRAF* mutations. The rare mucin-poor HP, nearly devoid of cytoplasmic mucin, may have increased nuclear atypia. It remains unclear as to whether histologic subtyping of HPs has clinical utility and therefore, current guidelines advise against doing so in routine clinical practice.

Sessile serrated adenoma/polyp (SSA/P)

SSA/Ps, like hyperplastic polyps, have serrated crypts but the SSA/P crypts are distorted with widened, branching bases that are a typical feature (Figure 1B)³. Dysplasia, seen in conventional adenomas, is not a feature of SSA/Ps, but focal dysplasia may develop during tumor progression^{3, 6}. The presence of typical dysplasia classifies the polyp as SSA/P with dysplasia (Figure 1C), which may represent an intermediary in molecular progression of SSA/P to malignancy⁷. Colectomy specimens from CRC patients show serrated polyps more frequently with tumors showing microsatellite instability (MSI)⁸. These data were often obtained before recognition of SSA/Ps as a distinct entity, and re-review of the histology has suggested that many of these lesions were SSA/Ps⁹. When a remnant SSA/P is found adjacent to carcinoma, a transition zone of dysplasia is frequently present⁹. Molecular

profiling of SSA/Ps indicates that dysplastic areas are likely the immediate precursors of CRCs that show MSI¹⁰.

Traditional serrated adenoma (TSA)

TSAs are also serrated, but have villiform projections lined by hypereosinophilic cells¹¹. Premature crypt formation perpendicular to the longitudinal axis of the villus, is a characteristic histologic feature known as ectopic crypt formation, whereby the crypts have lost anchoring to the underlying muscularis mucosae^{11, 12} (Figure 1D). In some TSAs, cytologic dysplasia is present, but in others, pale pink cells with minimal cytologic changes represent metaplastic, non-proliferating senescent cells exist^{3, 9}. The TSA is a poorly understood histologic entity. The molecular characterization of TSAs has shown polyps with either *KRAS* or *BRAF* mutations that suggest distinct variants despite overlapping morphologic features¹³.

III. Molecular Features of the Serrated Neoplasia Pathway

Most CRCs develop from conventional adenomas through a molecular pathway characterized chromosomal instability (CIN). However, approximately 15% of CRCs develop through an alternate pathway characterized by defective DNA MMR that gives rise to high frequency MSI (MSI-H). MSI was first described in association with Lynch syndrome (hereditary nonpolyposis colorectal cancer - HNPCC) due to germ-line mutations in MMR genes. In sporadic CRCs, MSI is a consequence of defective MMR due to hypermethylation of the *MLH1* MMR gene that frequently occurs in a background of increased methylation of CpG islands in gene promoter regions known as the CpG island-methylator phenotype (CIMP)¹⁴⁻¹⁶. CIMP is not exclusive to MSI tumors since it is infrequently found in tumors lacking *MLH1* methylation or MSI¹⁷. Thus, CIMP CRCs include almost all sporadic cases with MSI and a proportion of CRCs that are microsatellite stable (MSS)^{15, 17, 18}. About 40% of CRCs with MSI and *MLH1* hypermethylation carry hotspot mutations (V600E) in codon 15 of the *BRAF* oncogene^{17, 19}. Mutations in *BRAF* result in activation of the mitogen-activated protein kinase (MAPK) pathway that promotes cell proliferation and survival.

The improved histological classification of serrated polyps has enabled a comparison of molecular features based upon polyp subtype. It is believed that most CRCs with the CIMP phenotype evolve through the serrated neoplasia pathway^{20, 21}. A clear link has been found between serrated polyps, especially SSA/Ps, and sporadic CRCs showing MSI and CIMP¹⁸. Using a specific marker panel¹⁸, CIMP was detected in 7% of microvesicular HPs and in 48% of advanced serrated polyps²². CIMP positivity is frequent in proximal SSA/Ps,⁹ and SSA/P histology has been seen at the margins of MSI CRCs^{9, 23}. If hypermethylation inactivates *MLH1* early in the serrated pathway, then an MSI-H CRC will result.

BRAF and *KRAS* mutations are early molecular alterations in serrated lesions²⁴ and are mutually exclusive in colorectal neoplasms¹⁶. A simplified diagram of these two serrated pathways is shown in Figure 2. CIMP has been shown to be strongly associated with point mutations in *BRAF*²⁵. *BRAF* mutation is an early event in the serrated pathway being detected frequently in microvesicular HPs and in most SSAs that also display a high level of CIMP⁵. In contrast, *BRAF* mutations are not found in conventional adenomas²⁵. Importantly, neither *BRAF* mutations nor CIMP are found in CRCs with germline MMR mutations that result in Lynch Syndrome, thereby, highlighting their association with the serrated pathway. Taken together, these findings support the notion that SSA/Ps are the precursor lesions of sporadic MSI CRC. While this end-point does intersect with the end-point in Lynch syndrome, it is important to remember that the major precursor lesion of CRCs in Lynch syndrome is the adenoma, not a serrated polyp.

Compelling evidence supports a serrated neoplasia pathway with SSA/Ps bearing *BRAF* mutations as precursors of MSI-H and/or CIMP-high CRCs^{5, 25}. A second pathway involves CIMP-low and MSS cancers that are associated with *KRAS* mutations. A precursor lesion of this second pathway may be the TSA. An additional feature of this second putative serrated pathway is silencing of the DNA repair gene methylguanine methyltransferase (MGMT) by promoter hypermethylation which has been associated with *KRAS* mutation and CIMP-low status^{26, 27}. Further support for at least two serrated neoplasia pathways is the finding that *KRAS* and *BRAF* mutations segregate with lesion type, i.e., polypoid vs flat, respectively²⁸. *KRAS* mutations are common in rectal and polypoid TSAs²⁹, but are rare in SSA/Ps²⁵. It is believed that some microsatellite stable (MSS) adenocarcinomas may originate from TSAs. In aggregate, data suggest that approximately 30% of colonic adenocarcinomas derive from the serrated neoplasia pathway¹⁰.

IV. Epidemiology of Serrated Polyps

By far, the most common serrated polyp is the conventional hyperplastic polyp which accounts for 70–95% of all serrated polyps^{30, 31} and most frequently occurs in the recto-sigmoid colon³¹. SSA/Ps account for 5–25% of serrated polyps and occur predominantly in the proximal colon^{30–33}. While the prevalence of SSA/Ps varies depending on the clinical study, the overall prevalence varies from 2% – 9%^{30–33}. However, a recent study evaluating the prevalence of serrated polyps in the proximal colon in average-risk individuals undergoing screening colonoscopy found the prevalence of SSA/Ps to be as high as 20%³⁴. TSAs are much less common than SSA/Ps and account for only < 1% of all colorectal polyps^{30, 31}. TSAs typically occur in the distal colon and rectum, and tend to have a pedunculated or broad-based polypoid growth pattern when compared with SSA/P²⁹.

Although uncommon, TSAs are likely precursor lesions to some CRCs as suggested by Longacre and Fenoglio-Preiser who showed that 11% of TSAs contain intramucosal carcinoma³⁵.

The primary risk factors for serrated neoplasia are common to subjects with conventional adenomas and include the combined effects of inherited (genetic) susceptibility and environmental factors. Environmental factors that increase the risk for serrated neoplasia include lifestyle and diet. In a study by Wallace et al, obesity, dietary fat, cigarette smoking, total energy intake, and red meat were associated with an increased risk of serrated polyps in the left colon; whereas, a family history of polyps and folate treatment were associated with an increased risk of serrated polyps in the proximal colon³⁶. Cigarette smoking is associated with an increased risk of conventional adenomas and CRC. Studies examining the association of cigarette smoking and incident CRC have found that smokers have a significantly higher risk of tumors with MSI, CIMP, and *BRAF* mutations³⁷. These molecular features, characteristic of SSA/Ps, suggest that cigarette smoking increases CRC risk via the serrated neoplasia pathway.

Jeevaratnam et al.³⁸ first described the possibility of a familial serrated polyposis syndrome in 1996. Subsequently, cases of hyperplastic polyposis with synchronous adenocarcinoma were reported and it is now recognized that individuals with hyperplastic polyposis present with synchronous cancers of the colorectum in up to 25– 50% of cases^{26, 39–43}. Recently, the term ‘hyperplastic polyposis’ has been changed to ‘serrated polyposis’ since a spectrum of serrated lesions, not just hyperplastic polyps⁴¹, can be found in this condition as discussed below.

V. Serrated Polyposis Syndrome

The recently modified WHO clinical criteria for the diagnosis of serrated polyposis includes any one of the following: 1) at least five histologically diagnosed serrated polyps proximal to the sigmoid colon, two of which are greater than 1 cm in diameter, or 2) any number of serrated polyps occurring proximal to the sigmoid colon in an individual having a first-degree relative with serrated polyposis, or 3) more than 20 serrated polyps of any size but distributed throughout the colon⁴. These criteria suggest that serrated polyposis may encompass a group of diseases rather than being a single entity, or represent a disease continuum.

The exact prevalence of SPS is unknown and it is under-recognized by endoscopists given lack of familiarity with SPS criteria and the need for more consistent application of such criteria in individual patients⁴⁴. The mean age at diagnosis of SPS is 52 years^{39, 45, 46}; however, the age at diagnosis is quite variable among studies^{41, 47}. Approximately 5% of patients with SPS have at least one first-degree family member with the condition^{41, 46}. Autosomal dominant and recessive inheritance of SPS has been suggested^{38, 41, 43, 48} with a 5-fold increased risk of CRC noted in first-degree relatives of SPS patients³⁹. Further evidence that SPS has a heritable component is the finding that both first- and second-degree relatives of index patients are at increased risk of CRC, and that first-degree relatives are at significantly increased risk of pancreatic cancer⁴⁹. Despite these observations, an underlying genetic basis for SPS has yet to be defined. Molecular analysis of serrated neoplasms from patients with SPS reveals the presence of CIMP as well as *BRAF* mutations that reflect the serrated pathway^{24, 31, 50}. Interestingly, patients with *MUTYH*-associated polyposis can have a similar colonic phenotype as SPS with the finding of concomitant adenomas and serrated neoplasms⁵¹. However, serrated polyps are molecularly distinct from those found in patients with *MUTYH*-associated polyposis in that they show *KRAS* mutations, but lack CIMP and *BRAF* mutations⁵¹.

VI. Clinical Implications

The recognition of a serrated neoplasia pathway to CRC has important clinical implications for detection, surveillance, and treatment. While management of colonic serrated neoplasia should be based on the natural history and malignant potential of the various subtypes of serrated polyps, such data are limited as studies were performed prior to the distinction among serrated polyp subtypes. A critical yet unanswered question is whether certain serrated polyp subtypes, especially SSA/Ps, can progress to invasive cancer at a rate that is similar to or more rapid than conventional adenomas.

Studies by Jass et al⁵² suggested that progression via the serrated pathway can rapidly lead to malignant transformation. Potential for rapid malignant transformation was suggested by a review of 8 cases of invasive MSI CRCs and high-grade dysplasia arising from SSA/Ps (less than 1cm) showing cytologic dysplasia in the proximal colon⁵³. In addition, this study found the interval from SSA/P to adenocarcinoma was less than 3 years in 18% and 3–6 years in 27% of cases. Lazarus et al⁵⁴ showed a higher growth rate and rate of recurrence for SSA/Ps compared to conventional adenomas, suggesting that this serrated subtype may be more aggressive. In contrast, a recent and large cross-sectional study reported that the median age of patients with SSA/Ps was 61 years and those with serrated cancers was 76 years, suggesting a more indolent behavior of these serrated neoplasms³². It is known that the epigenetic inactivation of *MLH1* in sporadic MSI CRCs is associated with older age at diagnosis⁵⁵. Inactivation of *MLH1* occurs in precursor SSA/Ps and these lesions are prone to acquire additional mutations^{56, 57}. It is important to make the distinction between age at diagnosis and rapidity of progression to carcinoma.

Interval cancers, i.e., cancers occurring after a previous colonoscopy, represent either missed cancers, interval development of cancer due to missed polyps, incompletely removed polyps, or rapid progression of serrated polyps to cancer. Importantly, interval (or missed) cancers have been shown to be four times more likely as non-interval cancers to show MSI and CIMP which are both molecular signatures of the serrated neoplasia pathway^{21, 58}. These data suggest that the serrated pathway may contribute disproportionately to interval or missed cancers. Evidence also suggest a greater risk of synchronous and metachronous neoplasia including CRC in individuals with SSA/Ps. In this regard, Schreiner et al showed that the presence of a proximally located or large (>10mm) SSA/Ps was an independent risk factor for the presence of CRC. In addition, the presence of large serrated polyps increases the risk for CRC, especially in the proximal colon^{7, 59}. These data indicate the importance of removing all serrated lesions, with the exception of diminutive hyperplastic polyps in the rectosigmoid colon.

VII. Detection of Serrated Polyps

Serrated polyps are less likely than conventional adenomas to bleed, so fecal occult blood testing may not detect these lesions⁶⁰. While there no data regarding the sensitivity and specificity of computed tomographic colonography to detect serrated polyps, the sessile and flat morphology of these lesions suggest that that this modality would perform poorly. Optical colonoscopy appears to the best of the current screening methods to detect serrated polyps⁶⁰; however, significant challenges remain. Colonoscopy with polypectomy has been shown to significantly reduce the incidence of CRC; however, recent data indicate that it is substantially less effective at preventing proximal colon cancers^{61–64}. Furthermore, interval CRCs are three times more likely than non-interval cancers to occur in the proximal colon and four times more likely to show MSI⁵⁸. Failure to recognize and adequately remove neoplastic polyps including serrated lesions, are important factors associated with interval cancers. Differences in endoscopic appearance and detection of proximal versus distal colorectal neoplasms may explain variation in the effectiveness of colonoscopy for CRC prevention⁶⁵. Colonoscopy is better at detecting large and polypoid lesions whereas serrated polyps tend to be more subtle. Available evidence suggests that serrated neoplasms, particularly proximal SSA/Ps, may be important contributors to the reduced efficacy of colonoscopy for the prevention of proximal bowel cancers and for interval cancers.

Typical hyperplastic polyps are usually small (<5 mm), slightly raised, and occur most frequently in the rectosigmoid colon³¹. These polyps tend to flatten and are difficult to visualize when the lumen is fully distended. Differentiating hyperplastic polyps from adenomas using white-light endoscopy can be challenging and narrow band imaging may help with this distinction⁶⁶. Diminutive hyperplastic polyps in the rectosigmoid colon have a negligible (if any) potential for malignancy. In contrast, SSA/Ps are usually larger than adenomas with 50% being >10 mm in size and frequently located in the proximal colon⁶⁷. SSA/Ps are endoscopically subtle lesions, often flat to sessile with indistinct edges and similar color as the surrounding mucosa. The surface is soft, smooth-appearing, pale and with minimal vascularity. Adherent mucus covering the polyp is frequent and can appear yellow, green, or even rust-colored^{21, 25} (Figure 3A and B). Removing the adherent mucus cap can be difficult but reveals the underlying lesion (Figure 3C–F). When visualized with narrow-band imaging they appear red in color (Figure 4A and B). In contrast, TSAs typically occur in the distal colon and rectum and tend to be pedunculated or broad-based⁶⁸ making endoscopic detection less difficult.

In an analysis of 158 SSA/Ps⁶⁹ observed during routine colonoscopy, the following visual descriptors were most prevalent for SSA/Ps: mucus cap, rim of debris or bubbles (Figure 3C), alteration of the contour of a fold (Figure 3A and F), and interruption of the underlying

mucosal vascular pattern⁶⁹. The mucus cap was the most prevalent endoscopic feature seen in 64% of lesions⁶⁹ with an “egg-drop soup” appearance (Figure 3C). By Paris Classification⁷⁰, 98% of serrated lesions were flat and the vast majority of SSA/Ps were minimally elevated (Paris Class 0-IIa). A rim of debris, mucus cap, and obscuration of the vasculature were more common with SSA/Ps whereas conventional adenomas were more likely to be nodular, red, and dome-shaped⁶⁹. The subtle and varied endoscopic features of SSA/Ps make them inconspicuous compared to pedunculated and/or protruding polyps and are, therefore, easily overlooked^{33, 71}.

Detection of proximal serrated polyps during screening colonoscopy has been shown to be operator dependent and to correlate with adenoma detection rates^{33,71}. In fact, a major factor in the detection of SSA/Ps is the diligence and experience of the endoscopist⁷¹. Some endoscopists overlook >half of serrated lesions in the proximal colon^{33, 71}. Burnett-Hartman et al conducted a case-control study⁷² showing that endoscopy protected from advanced adenomas, but no statistically significant association was found between previous endoscopy and SSA/Ps⁷². Together, these data suggest failure to detect SSA/Ps is a likely contributor to the lower level of protection afforded by colonoscopy for the prevention of proximal vs distal colon cancers⁷³. The extent to which detecting CRCs associated with SSA/Ps is related to rate of progression to malignancy is unknown. Regardless, increased familiarity with the subtle endoscopic appearances of SSA/Ps will likely improve detection and may improve the ability of colonoscopy to prevent CRC.

To optimize the colonoscopic detection of sessile serrated polyps, strict adherence to the following are required: a high-quality bowel preparation, adequate luminal distention at colonoscopy with careful and complete mucosal inspection, diligent washing to remove debris, and slow colonoscopic withdrawal^{74, 75}. Chromoendoscopy is an adjunctive technique that has the potential to improve detection of serrated polyps in the proximal colon³¹. Chromoendoscopy uses a contrast agent, frequently indigo carmine, that is sprayed on the colonic mucosa during endoscopy and accumulates in colonic pits and grooves, thereby, highlighting flat lesions and aiding in differentiating non-neoplastic from neoplastic polyps. To enhance the endoscopic recognition of serrated polyps, Kimura et al⁷⁶ evaluated magnifying chromoendoscopy that identified a novel pit pattern, referred to as Type II-open (Type II-O). This pit pattern was only moderately sensitive (65%) but highly specific (97%) for identifying SSA/P. Type II-O pits are similar to Type II pits in the Kudo classification of pit patterns⁷⁷, but are wider and rounder in shape. Since the main issue is one of identifying SSA/Ps, the limited sensitivity of pit pattern analysis limits the clinical utility of this approach. The role of chromoendoscopy and other adjunctive imaging methods, including narrow-band imaging and autofluorescence for improving the detection of serrated polyps, await further study. Interestingly, a recent study showed that stool DNA testing using methylated vimentin and mutated *BRAF* genes was able to detect SSA/Ps, suggesting that this noninvasive technology may have a role in the detection of serrated lesions⁷⁸.

Surveillance

As for conventional adenomas, CRC risk in patients with serrated polyps is dependent upon polyp size, number, and pathologic features. In contrast to conventional adenomas, however, the anatomic distribution of serrated polyps is more strongly associated with CRC risk. Specifically, large (> 1 cm) serrated polyps were the strongest predictor of CRC, particularly for proximal CRCs, in a study of 10,199 subjects in Japan undergoing their first colonoscopy⁵⁹. These and other data indicate that risk stratification for serrated polyps can be performed using polyp size and location, as well as the presence or absence of dysplasia. To date, however, limited post-polypectomy longitudinal data exist upon which to base surveillance intervals after removal of serrated polyps, and current recommendations for post-polypectomy surveillance of serrated lesions are based on expert opinion^{9, 79, 80}.

Recommendations for serrated polyps have been incorporated into recent guidelines for colonoscopy surveillance after screening and polypectomy in the United States (Table 2)⁸¹. The typical, small (<10mm), hyperplastic polyps of the rectosigmoid are very low risk lesions and do not require intensification of colonoscopy surveillance (interval 10 years). Non-dysplastic SSA/Ps less than 1 cm in size can be surveyed at 5-year intervals. Serrated polyps with any of the following three features require surveillance colonoscopy in 3 years: size ≥10mm, presence of cytological dysplasia, or traditional serrated adenoma. After piecemeal resection of a SSA, individuals should have a repeat colonoscopy in 3–6 months to evaluate the polypectomy site for residual or recurrent polyp as per conventional adenoma guidelines to ensure complete resection. Surveillance intervals may require modification based on age, family or personal history of CRC, and comorbidities. A limitation of these surveillance recommendations is underscored by patients with SSA/P and cytologic dysplasia, where a 3 year colonoscopic surveillance interval has been recommended. The appropriateness of this interval can be questioned given that SSA/Ps with cytologic dysplasia show frequent MSI and have the potential to rapidly progress to carcinoma^{53, 57}. Therefore, managing SSA/Ps with dysplasia in a manner similar those with advanced adenomas with repeat colonoscopy at one year after initial complete resection would be reasonable at this time⁵⁶. Current surveillance guidelines for serrated polyps will undoubtedly be updated as higher quality evidence becomes available.

The highest risk group is patients who meet criteria for the serrated polyposis syndrome whereby colonoscopy should be performed yearly with the intent to remove all proximally located serrated lesions or all serrated polyps ≥5 mm in size if there are numerous diminutive lesions. If endoscopic control of serrated polyposis is not feasible, then surgery is indicated for high polyp burden. The most common surgical procedures are extended right hemicolectomy or subtotal colectomy. Annual endoscopic surveillance of the residual colon and/or rectum is indicated.

Treatment

All colorectal polyps, with the exception of small hyperplastic-appearing polyps in the rectosigmoid, should be completely removed. Incomplete polypectomy and/or missed lesions likely account for a large percentage of interval cancers. Incomplete polypectomy and lack of adherence to follow-up surveillance were shown to be strongly associated with colorectal cancer risk after colonoscopic polyp detection in a community setting⁸². The issue of complete polypectomy is particularly important for SSA/Ps since frequent positive margins indicates their incomplete removal⁸³. To ensure complete polyp excision, snare technique is recommended for polyps larger than 3 mm in size. Attempting to remove polyps greater than 4 mm in size with multiple biopsies should be avoided, as it is an ineffective polyp removal technique. When removing large sessile polyps, cauterization of the perimeter of the polypectomy site can decrease the rate of incomplete resection. If repeat attempts at colonoscopic polypectomy fail, surgical resection should be considered.

VIII. Conclusion

Recognition of the serrated neoplasia pathway represents an important advance in understanding CRC carcinogenesis with opportunities for prevention. Serrated colorectal polyps are clinically and molecularly diverse lesions that share common crypt luminal morphology characterized by glandular serration. Evidence indicates that subtypes of serrated polyps, particularly TSA, SSA/P, and SSA/P with dysplasia, may progress to adenocarcinoma through a serrated neoplasia pathway. Furthermore, data suggest that SSA/Ps are precursors of MSI colon cancers and may undergo more rapid progression to malignancy. SSA/Ps and MSI-H colon cancers are more common in the proximal colon and colonoscopy has been shown to be relatively ineffective in preventing proximal colon

cancers, potentially due to missed serrated polyps. The malignant potential of the serrated neoplasia pathway is acknowledged by the inclusion of serrated polyps in recent colonoscopy surveillance guidelines. A critical step to decreasing CRC incidence via the serrated pathway is to improve detection of serrated lesions and to ensure their complete removal at endoscopy.

Abbreviations used

CIMP	CpG island-methylator phenotype
CRC	Colorectal carcinoma
MMR	mismatch repair
MSI	microsatellite instability
SPS	serrated polyposis syndrome
SSA/P	sessile serrated adenoma/polyp
TSA	traditional serrated adenoma
WHO	World Health Organization

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Figure 1.

Histomicrographs of serrated polyps. A, Hyperplastic polyp (microvesicular subtype) with serrations in the upper half of the crypt and no cytologic dysplasia. B, Sessile serrated adenoma/polyp (SSA/P) with characteristic branching crypt bases (arrow). C, SSA/P with dysplasia: arrow indicates dysplastic epithelium with hyperchromatic nuclei and pseudostratification. D, Traditional serrated adenoma showing ectopic crypt (arrow and circle).

Figure 2.

Diagram of two potential molecular pathways of serrated neoplasia. The precursors of the first pathway are the microvesicular hyperplastic polyp and/or the sessile serrated adenoma/polyp (SSA/P) with the potential for SSA/P to arise de novo from normal mucosa. This pathway results in cancers that are CIMP-high and carry *BRAFV600E* mutations with either MSI or MSS status. The second pathway is less defined with the potential precursor lesion being the goblet cell hyperplastic polyp and the traditional serrated adenoma (TSA). The end result of the second path is MSS and CIMP-low cancers that are associated with *KRAS* mutations, although this remains speculative. Abbrev.: CIMP, CpG Island methylator phenotype; MSI, microsatellite instability; MSS, microsatellite stable;

Figure 3.

Endoscopic photographs demonstrating the varied morphologic appearances of SSA/Ps. *A*, SSA/P with indistinct edges which overlies a mucosal fold that alters its contour. *B*, SSA/P in the ascending colon with a rim of debris. The lesion is shown to obscure the course of a submucosal vessel (arrow). *C*, SSA/P at the hepatic flexure is covered by a debris-stained mucus cap which has the characteristic “egg-drop soup” appearance. *D*, Lesion in *C* is shown after washing off the mucus cap. The SSA/P displays a subtle appearance with blurring of submucosal vessel and mucosal irregularity. *E*, Large SSA/P is obscured by mucus debris. *F*, Lesion in *E* after washing and aspiration of intraluminal air displays more conspicuous nodularity.

Figure 4.
Endoscopic photographs of SSA/P. *A*, SSA/P in ascending colon with an adherent mucus cap in white light. *B*, Lesion in *A* under narrow-band imaging.

Table 1WHO Classification of Serrated Polyps^a

Non-dysplastic	Dysplastic
<u>Hyperplastic polyps:</u> <ul style="list-style-type: none"> Goblet cell hyperplastic polyp (GCHP) Microvesicular hyperplastic polyp (MVHP) Mucin poor hyperplastic polyp (MPHP) 	Sessile serrated adenoma/polyp (SSA/P) with dysplasia
Sessile serrated adenoma/polyp (SSA/P)	Traditional serrated adenoma (TSA)

^aSee Snover et al.⁴

Table 2Surveillance Guidelines for Serrated Polyps^a

Lesion found	Surveillance interval (yrs)
Serrated polyposis	1
Sessile serrated polyp ≥ 10 mm	3
Sessile serrated polyp with cytological dysplasia	3
Traditional serrated adenoma	3
Sessile serrated polyp(s) <10 mm with no dysplasia	5
Small (<10mm) hyperplastic polyps in rectosigmoid	10

^aSee Lieberman et al.⁸¹