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Serrated Lesions of the Colorectum: Review and Recommendations From an Expert Panel

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Abstract

Serrated lesions of the colorectum are the precursors of perhaps one-third of colorectal cancers. Cancers arising in serrated lesions are usually in the proximal colon, and account for a disproportionate fraction of cancer identified after colonoscopy.

We sought to provide guidance for the clinical management of serrated colorectal lesions based on current evidence and expert opinion regarding definitions, classification and significance of serrated lesions. A consensus conference was held over 2 days reviewing the topic of serrated lesions from the perspectives of histology, molecular biology, epidemiology, clinical aspects, and serrated polyposis.

Serrated lesions should be classified pathologically according to World Health Organization criteria as hyperplastic polyps, sessile serrated adenoma/polyp (SSA/P) with or without cytological dysplasia, or traditional serrated adenoma (TSA). SSA/P and TSA are premaligant lesions, but SSA/P is the principle serrated precursor of colorectal cancers.

Serrated lesions have a distinct endoscopic appearance, and several lines of evidence suggest that on average they are more difficult to detect than conventional adenomatous polyps. Effective colonoscopy requires an endoscopist trained in the endoscopic appearance of serrated lesions. We recommend that all serrated lesions proximal to the sigmoid colon and all serrated lesions in the rectosigmoid > 5 mm in size, be completely removed. Recommendations are made for post-polypectomy surveillance of serrated lesions and for surveillance of serrated polyposis patients and their relatives.

Keywords

serrated lesions; colon; rectum; colonoscopy; colorectal polyps; colorectal cancer

Introduction

Serrated lesions of the colorectum are characterized histologically by a serrated (or sawtoothed) appearance of the crypt epithelium (Figure 1a–c). Thirty years ago serrated lesions were called “hyperplastic” polyps and were thought to have no malignant potential (1). Since then a subset of serrated lesions has been established as the precursors of a group of colorectal cancers (CRCs) that exhibit hypermethylation and arise primarily in the proximal colon, and which may account for one-third of all CRCs (2–11). Subtypes of serrated lesions (Table 1) have different molecular profiles and variable potential to develop into CRC (12–19).

The purposes of this consensus report are to summarize the pathologic, molecular, and endoscopic features of serrated lesions, to increase awareness of the threat posed by these lesions, to describe the endoscopic appearance of these lesions, to stress the importance of accurate detection and complete excision, and to provide recommendations regarding post-resection management. Table 2 summarizes the key concepts and recommendations in this article.

Methods

This statement is the result of a two day consensus meeting held in Cleveland in 2010 and sponsored by the National Institutes of Health. The panel members were chosen for their expertise in endoscopy, surgery, pathology, epidemiology, and/or molecular aspects of serrated lesions and/or serrated polyposis. In preparation of this report a literature review was conducted in MEDLINE, 1996 to October, 2011, using the terms hyperplastic polyp, serrated polyp, serrated adenoma, serrated cancer, hyperplastic polyposis syndrome, serrated polyposis syndrome, microsatellite instability, CpG Island Methylator phenotype, and hypermethylation.

The recommendations presented here generally and necessarily reflect expert consensus opinion, as the levels of evidence available to support recommendations are of low or very low quality (20). The review and recommendations reported here were not commissioned, reviewed, or endorsed by the American College of Gastroenterology.

Pathology of serrated lesions

Overview

Serrated lesions of the colorectum are currently classified by the WHO into three general categories (19) (Table 1). The rationale for the terminology in Table 1 has been described previously (11, 21). The terms “sessile serrated adenoma” and “sessile serrated polyp” are considered synonyms, and both are acceptable.

In general, the subtypes of serrated lesions are identified by cytological and architectural features and by the location and extent of the proliferative zone (14, 21) as described below. The specific causes of the cytological, architectural, and proliferative alterations are not known, but they are presumed to result from epigenetic alterations in genes responsible for cell proliferation and differentiation (caused by hypermethylation of promoter DNA), as well as genetic changes such as mutations in *BRAF*.

Hyperplastic polyps

HPs are characterized by the presence of straight crypts which extend symmetrically from the surface of the polyp to the muscularis mucosae without significant distortion (Figure 1a–c). The crypts are typically wider at the polyp surface compared to the base, and do not show horizontal or irregular branching (Figure 1a–c). Similarly, the degree of “serration” is more pronounced in the upper half and surface of the polyps than at the base. Depending on the subtype (see below), the epithelium may be lined with a variety of cell types including microvesicular mucinous cells, goblet cells and undifferentiated cells. Neuroendocrine cells are often prominent at the base of the polyp. In general, mitoses are confined to the basal half of the polyp. In many cases, the basement membrane underneath the surface epithelium is thickened as well. Only minimal cytological atypia is present in HPs. The cells show small oval or slightly elongated nuclei, without stratification or hyperchromaticity. It is important to consider overall architecture, since cytological atypia without significant architectural changes may be due to regenerative changes in an inflamed hyperplastic polyp.

HPs can be subdivided histologically into microvesicular (MVHP), goblet cell (GCHP), and mucin poor (MPHP) types based on the characteristics of lining epithelium. MPHPs are rare, and little is known about their molecular features or natural history. MVHPs and GCHPs are well characterized and display considerable differences in molecular and histologic features as well as anatomic distribution within the colon. Although we describe the pathologic features of these HP subtypes, any clinical importance of the distinctions is currently uncertain.

MVHPs are characterized by the presence of small droplet ("microvesicular") mucin within the cytoplasm of most cells. Scattered goblet cells are common as well (Figure 1a). MVHPs are located predominantly in the left colon, although 10–15% occur in the transverse and right colon. Multiple MVHPs are common, particularly in the rectum.

In contrast to MVHPs, GCHPs are characterized by the nearly exclusive presence of goblet cells (Figure 1b). Cells with microvesicular mucin are not present. Compared to MVHPs, GCHPs show few or no luminal serrations. Although the proliferative zone remains located in the basal portion of the crypts, it is often limited to only a few cells. GCHPs are also more common in the left colon (≈90%), and are typically very small (< 0.5 cm).

MPHPs show little or no cytoplasmic mucin. They have a luminal serration pattern similar to MVHPs, but also reveal increased nuclear atypia in the form of large, round, hyperchromatic nuclei, but without pseudostratification (Figure 1c). One theory is that MPHPs represent injured MVHPs with inflammation and reactive epithelial changes.

Sessile serrated adenoma/polyp

SSA/Ps are characterized by the presence of a disorganized and distorted crypt growth pattern which is usually easily identifiable upon low power microscopic examination (14, 21) (Figure 2a). Crypts, particularly at the basal portion of the polyp, may appear dilated and/or branched, particularly in the horizontal plane, which leads to the formation of "boot," "L," or "anchor"-shaped crypts (Figure 2a). The basal half of the crypts often contain excessive ("hyper") serration and mature goblet cells and mucinous cells. Upon Ki67 staining (a stain for proliferating cells), positive cells may be located anywhere in the crypt from the base to the surface, and often in an irregular and asymmetric pattern (21). Other common cytological features include various degrees of nuclear atypia (e.g., cells with open nuclei and prominent small nucleoli), dystrophic goblet cells, and an absence of neuroendocrine cells. Foci of cells with elongated penicillate nuclei and eosinophilic cytoplasm that are reminiscent of cells seen in TSAs (see below) may be present. SSA/Ps often produce excessive extracellular mucin, and it is not unusual to see mucin fill the lumen of dilated crypts and coat the surface of the polyp. Some SSA/Ps show prominent lipoma-like adipose tissue in the submucosa, but it is unclear if this phenomenon represents a chance association of SSA/P with a submucosal lipoma or some form of epithelial-mesenchymal interaction. Herniation of crypts through the muscularis mucosae, giving rise to a "pseudoinvasive" or "inverted" growth pattern, is not unusual, but the pathogenesis of this finding is unknown. Pseudoinvasion can also be seen in hyperplastic polyps and therefore, while more common in SSA/Ps, is not pathognomonic of SSA/P.

Differential Diagnosis: Microvesicular Hyperplastic Polyp (MVHP) vs Sessile Serrated Adenoma (SSA/P)

Serrated lesions may show MVHP pathology in one area and SSA/P morphology, such as dilated and irregular crypts, in another. These lesions have been sometimes interpreted as evidence of progression of MVHP to SSA/P, but MVHP-like features could simply be part of the histologic spectrum of SSA/P. A difficult and unresolved diagnostic problem relates to polyps that show nearly exclusive MVHP morphology, but in addition show only a few (or even just one), irregular, hyperdilated and distorted crypts of the type seen in SSA/P. Unfortunately, the minimum criteria necessary to establish a diagnosis of an SSA/P have not been set. We recommend that the presence of at least one unequivocal architecturally distorted, dilated, and/or horizontally branched crypt, particularly if it is associated with inverted maturation, is sufficient for a diagnosis of SSA/P. In clinical practice there is substantial interobsever variation among pathologists in the differentiation of SSA/P from

HP, and agreement between pathologists is moderate at best, including between expert pathologists (22–24).

Sessile serrated adenoma/polyp (SSA/P) with cytological dysplasia

Recent data suggest that SSA/P with foci of conventional (tubular or tubulovillous) adenoma-like dysplasia represent progression towards carcinoma. Preliminary evidence indicates that a substantial portion of these lesions demonstrate inactivation of the mismatch repair gene *MLH1*, and the dysplastic areas often demonstrate microsatellite instability (25). Such lesions were previously reported in the literature as "mixed hyperplastic/adenomatous polyps". The term "mixed polyp" is discouraged because it doesn't convey the concept that combined features represent progression of an SSA/P towards carcinoma, and that the cytologically dysplastic portion has different molecular characteristics from conventional adenomas.

Histologically, SSA/Ps with conventional adenoma-like dysplasia usually show a portion of the polyp with typical SSA/P morphology and another with an abrupt transition to cytologically dysplastic areas (Figure 2b). Conventional adenoma-like dysplastic areas are characterized by the presence of elongated cells with penicillate and hyperchromatic pseudostratified nuclei, amphophilic cytoplasm, and increased mitoses. The dysplastic areas look similar to a conventional tubular or tubulovillous adenoma cytologically. Although areas of conventional adenomatous dysplasia may show a range of cytological atypia with features similar to "low-grade" or "high-grade" dysplasia in a conventional adenoma, the significance of the grade of dysplasia in SSA/P has not been evaluated. We recommend that SSA/P with any conventional cytological dysplasia be considered an "advanced" polyp with clinical significance similar to high-grade dysplasia in conventional adenomas.

Although poorly studied, another form of "dysplasia" may rarely be seen in SSA/P, which is referred to here as "serrated dysplasia" (19). Some cases may show a proliferation of atypical cells that are more cuboidal in shape, have eosinophilic cytoplasm, enlarged round nuclei with open vesicular prominent chromatin, and prominent nucleoli in addition to increased mitoses. Although not particularly serrated in its architectural growth pattern due to the presence of prominent eosinophilic cytoplasm, some experts believe that serrated dysplasia is also a histologic biomarker of neoplasia progression (19).

Traditional serrated adenoma

Histologically, TSAs often show a complex and distorted tubulovillous or villous ("filiform") configuration (Figure 3). In many cases, the villi are elongated with bulbous tips, and have been termed filiform TSAs (26). A recent study described a characteristic pattern of budding of proliferative crypts situated perpendicular to the long axis of filiform or villous structures of TSAs (ectopic crypt formation) (21). The authors suggested that this phenomenon is related to loss of (normal) anchorage of crypts to the underlying muscularis mucosae. It is the most characteristic histologic feature of this type of polyp. The predominant cell in TSA has abundant eosinophilic cytoplasm and a basal or centrally placed slightly elongated nucleus with an open/even chromatin pattern. The epithelium is usually pseudostratified but shows little if any proliferative activity and is often interpreted as a form of dysplasia. There is some controversy as to whether this epithelium represents a type of "metaplasia" or "senescence" rather than true dysplasia since it differs from the more cytologically atypical and proliferative appearance of dysplastic epithelium in conventional adenomas. Although a prominent and characteristic feature of TSAs, this type of eosinophilic epithelium may also be present in SSA/P with or without conventional adenoma-like cytological dysplasia. Goblet cells may also be a component of serrated crypts in TSA, and in some cases are prominent.

Both conventional adenoma-like dysplasia and serrated dysplasia can be observed in TSA. With neoplastic progression, it is believed that TSAs acquire increasing degrees of cytological atypia prior to the development of carcinoma. However, there is no consensus on identification and grading of dysplasia in TSA. Until agreement is reached, conventional adenoma-like dysplasia should be graded similarly to the way it is graded in conventional adenomas (high-grade vs. low-grade). A recent study showed that 25% of TSAs from Korea had changes described as high grade dysplasia and 8% showed intramucosal adenocarcinoma (27). High-grade serrated dysplasia shows cells with strongly eosinophilic cytoplasm, but in contrast to the eosinophilic epithelium characteristic of many TSAs, these eosinophilic cells show increased size of the nuclei, hyperchromaticity, stratification, and increased mitotic activity. The luminal serrated growth pattern is often more exaggerated, complex, and distorted than typical TSAs. Some cases may show a mixture of both types of dysplasia (both serrated and conventional adenoma-like) within the same polyp or even within the same crypt/villous unit. The risk of malignancy in TSA, and the rapidity of progression to carcinoma, is unknown.

As discussed in the molecular section of this article, there is a greater heterogeneity in the molecular profile of TSA compared to SSA/P. This may be partly due to inconsistency in the diagnostic criteria used for this lesion.

Unclassifiable serrated polyps

Some “serrated” lesions may be difficult to classify into one of the above discrete categories. Aside from histologic difficulties due to overlapping features, logistical factors such as poor orientation of specimens, poor staining, severe cautery artifact, or insufficient tissue may impede the ability to establish a precise diagnosis. In such cases, the term “serrated polyp unclassified” is acceptable. However, pathologists should make their best attempt to determine whether dysplasia is present, even when the diagnosis is difficult.

Conventional tubular, tubulovillous, or villous adenomas may occasionally show areas with a serrated growth pattern. Unfortunately, the biological significance of these polyps has not been studied. They are generally distinguished from other types of serrated polyps by the absence of areas of SSA/P or TSA morphology. The term “conventional adenoma (tubular, tubulovillous, villous) with a serrated growth pattern” is an acceptable term for these lesions. A recent study identified a distinctive group of conventional adenomas that met the above criteria and additionally exhibited cystic glands and bright cytoplasmic eosinophilia (28). The authors reported these lesions to be *KRAS* and *BRAF* wild type and CIMP-low. In that study, polyps were found in patients with at least one synchronous SSA/P.

Molecular features of the serrated pathway of carcinogenesis

Every colorectal cancer has a unique molecular profile (29). However, there are at least three general molecular mechanisms by which genetic and epigenetic events can lead to CRC: chromosomal instability (CIN), defective DNA mismatch repair leading to microsatellite instability (MSI), and epigenetic DNA promoter hypermethylation leading to the CpG island methylator phenotype (CIMP). Although there can be overlap of these mechanisms within any single cancer, the dominant mechanism has distinct clinical associations including the type of benign precursor lesion. The epigenetic CIMP pathway is considered to be the major mechanism driving the serrated pathway to CRC.

Serrated polyp-carcinoma sequence: the epigenetic (hypermethylator) mechanism

This mechanism of colorectal carcinogenesis is based on abnormal promoter CpG island hypermethylation (29–36). Methylation of CpG islands within promoter regions of genes is a normal way of reducing gene expression. More methylation means less expression, and if

the gene being silenced is a tumor suppressor gene, then loss of function may facilitate carcinogenesis. The extent of promoter CpG island hypermethylation in neoplasms varies considerably. Hypermethylation of some genes occurs in most CRCs, but it is the global nature of the methylation that distinguishes the subset of tumors labeled "CIMP-high." CIMP-high can be detected in tumors by screening a panel of genes for the degree of methylation (30).

Silencing a gene through promoter hypermethylation is an "epigenetic" rather than a genetic event since it does not involve an alteration in DNA sequence. Clinical associations with CIMP-high CRCs include older age, female sex, and proximal tumor location (31).

Some CIMP-high CRCs resemble Lynch-associated CRCs in that they have loss of DNA mismatch repair capability, evidenced by the presence of MSI. In these tumors, mismatch repair function is lost by promoter hypermethylation of *MLH1* (one of several genes required for DNA mismatch repair) rather than by a germline mutation as occurs in Lynch syndrome. These sporadic MSI CRCs also have CIMP, and account for about 15% of all colon cancers and 4% of rectal cancers (29, 31). *BRAF* mutations are strongly associated with CIMP-high CRCs where they act as an alternative to the *KRAS* mutations that occur commonly in CIN cancers (35–38).

Recognition of these three broad molecular mechanisms underlying CRC (CIN, MSI, and CIMP) provides molecular tools with which to identify their respective precursor lesions (Table 3). Many studies have shown common molecular features between benign serrated lesions and CIMP-high CRCs (39–44). Some HPs and most SSA/Ps have *BRAF* mutations and are CIMP-high, and SSA/Ps with cytological dysplasia frequently have *MLH1* hypermethylation and MSI in their dysplastic foci. Although some conventional adenomas are CIMP-high (45, 46), it is less common than in SSA/Ps and conventional adenomas do not have *BRAF* mutations or MSI.

The association of molecular markers with the histologic subtypes of benign serrated lesions and CIMP-high tumors has led to the proposal of an HP → SSA/P → SSA/P with cytological dysplasia → cancer sequence (Figure 4). This sequence occurs most commonly in the proximal colon, though recent evidence indicates a progressive increase in CIMP-high, MSI-high, and *BRAF* mutations in each colon segment from rectum through ascending colon, suggesting that risk for CIMP-high tumors increases proximally in a continuous rather than dichotomous (colon divided at the splenic flexure) fashion (47).

TSAs are much less common than SSA/Ps, so there are fewer data on their molecular profile (16, 48). TSAs appear to be more molecularly diverse than SSA/Ps in that they may have either *KRAS* or *BRAF* mutations or neither, and either low or high levels of CIMP. TSAs typically do not show hypermethylation of *MLH1* or develop MSI, but they do commonly have hypermethylation of the DNA repair gene *MGMT* (O6-methylguanine-DNA methyltransferase) (49). *MGMT* promoter methylation has been associated with both CIMP-low and -high CRCs (50). Since some HPs do share molecular features of TSAs (*KRAS* mutations and CIMP) (Table 3), it has been suggested that the TSA pathway could diverge from the SSA pathway on the basis of *KRAS* vs *BRAF* mutations and/or *MLH1* vs *MGMT* hypermethylation within subsets of HPs. However, a definite precursor of TSA has not been established.

Epidemiology of serrated lesions

Knowledge of the epidemiology of serrated lesions is primarily derived from studies of "hyperplastic" polyps prior to the recognition of the three subtypes described above.

Autopsy studies demonstrate variable prevalence rates of serrated lesions but collectively indicate that 25–50% of white adults have one or more serrated lesions (51–58). Colonoscopic studies show similarly variable but lower prevalence rates (59–64). The overall prevalence of serrated lesions increases only slightly with age during adulthood (51–61) in contrast to conventional adenomas which increase sharply with age (51, 54, 58). Hyperplastic polyps are more common in men in some (51, 52, 54, 57, 58, 61, 65) but not all studies (59, 66, 67). Overall, serrated lesions are most common in the sigmoid colon and rectum (51–55, 66, 67), but the distribution varies by histological subtype. HPs account for 70–95% of all serrated lesions and are predominantly left-sided (66–70). SSA/Ps comprise 5–25% of serrated lesions and are predominately right sided (66–74). TSAs are much less common than SSA/Ps. In clinical studies the prevalence of SSA/Ps is generally less than 2% (72, 73).

Risk factors for serrated lesions

Distal serrated lesions are associated with cigarette smoking (61–63, 65, 75–77). Alcohol intake (59, 61, 75, 78, 79), fiber intake (75, 79), calcium intake (60, 78, 79), NSAID use (60, 75, 79), family history of colorectal cancer (59, 60, 65, 78, 79), and high body mass index (54, 55, 59, 75, 79) have had inconsistent associations with distal serrated lesions (60, 61, 75, 78, 79). Physical activity has been inversely associated with risk (79), at least in men (75), and folate intake has also been inversely associated with the risk of distal serrated lesions (78). There are scant epidemiological data regarding right-sided serrated polyps, but cigarette smoking has been associated with proximal (77, 80, 81) as well as distal (82) serrated lesions, and with an overall higher risk of SSA/Ps and large SSA/Ps (83).

Association between serrated lesions and adenomas

Autopsy studies show a correlation between numbers of adenomas and serrated lesions, although with different anatomic distributions for the two types of lesions (51, 54–56, 58). One endoscopic series reported no association between the presence of adenomas and serrated lesions (84). At most there is a modest association between distal serrated lesions and proximal adenomas (85). Individuals with SSA/P tend to harbor synchronous adenomas (67–70, 73), HPs (73), and other SSA/Ps (69). Both large and/or proximal serrated lesions have been associated with an increased risk of synchronous advanced conventional neoplasia (81), and advanced neoplasia has been associated with the presence of large serrated lesions (86, 87). Individuals with both SSA/Ps and conventional adenomas are older, harbor more numerous, larger, and more dysplastic SSA/Ps and conventional adenomas compared to individuals with only SSA/Ps or conventional adenomas (88). Any association between HPs and adenomas in Lynch syndrome has been inconsistent (89–92).

No consistent association has emerged between serrated lesions found on colonoscopy and subsequent adenoma risk in asymptomatic individuals (81, 93–98). Some studies have shown serrated lesions to be associated with a higher risk of metachronous serrated lesions, just as adenomas are associated with a higher risk of metachronous adenomas (93, 99, 100), though patients with serrated lesions and/or adenomas can demonstrate either type of lesion upon follow up.

Association between serrated lesions and cancer

Case reports describe development of colorectal cancer in serrated lesions left *in situ* (101, 102). There are numerous reported cases of carcinoma with residual SSA/P (103, 104). In a pathology series of 2416 SSA/Ps, 14% demonstrated cytological dysplasia and 1% showed cancer (72). The mean age was 61 years in patients with SSA/P without cytological dysplasia, 66 years in those with SSA/P with low-grade cytological dysplasia, 72 years in those with high-grade cytological dysplasia, and 76 years in those with SSA/P with cancer.

These findings suggested a mean interval of 15 years for progression of SSA/P without cytological dysplasia to cancer (72).

One autopsy study noted a stronger association between serrated lesions and colorectal cancer than between adenomas and cancer (105), which was also found in one endoscopic study (92).

SSA/P has been associated with synchronous colorectal cancers with MSI (106). Serrated lesions ≥ 1 cm in size, which were likely SSA/P in most cases, were strongly associated with synchronous cancer, particularly in the proximal colon (107). MSI-high cancers were more likely to be accompanied by serrated lesions than microsatellite stable cancers (108). Further studies are required to determine whether this association applies to both HP and SSA/P or predominantly to SSA/P. In addition, synchronous colorectal cancers have higher rates of CIMP-high, MSI, and *BRAF* mutation than occurs in solitary CRCs (109), suggesting that multiplicity is associated with the serrated pathway.

SSA/P has also been associated with an increased risk of metachronous cancer. In case series, a diagnosis of SSA/P carries more risk for subsequent cancer than a diagnosis of HP. In one study, when 55 patients with SSA/P were followed, five (12.5%) developed cancer during 7.2 years of follow-up compared to just one among matched controls with HP and tubular adenoma (68). Proximal colon cancers with MSI were associated with serrated lesions at previous colonoscopies, and increasing size of these polyps was associated with shorter intervals between polyp and cancer diagnosis (42).

Detection of serrated lesions

The most common serrated lesion is a diminutive left-sided, pale, sessile HP (110). Some have a translucent quality and may disappear upon air insufflation (111). Larger serrated lesions (SSA/P) are typically similar in color to the surrounding mucosa. SSA/Ps and HPs in the proximal colon are often covered by a tenacious mucus cap (Figure 5a). The mucus can cause the polyps to appear yellow, green or rust-colored and appear red on narrow band imaging (Figure 5a). Care should be taken when washing mucus off the polyp, since the underlying lesion can be difficult to detect without it (Figure 6a–h). A recent prospective endoscopic assessment of 158 SSA/Ps identified the mucus cap in 64% of lesions, a rim of debris or bubbles in 52%, alteration of the contour of a fold in 37% and interruption of the underlying mucosal vascular pattern in 32% (112).

A number of imaging techniques not usually in use in clinical practice in western countries allow reliable differentiation of conventional adenomas from serrated lesions in real time during colonoscopy (113). Reliable real time differentiation of HPs from SSA/Ps might not be achievable by endoscopic techniques that image the lesion surface since the characteristic histologic features of SSA/P are primarily in the crypt base. However, a recent study found that a modified Kudo pit designated Type II-O is specific but not sensitive for SSA/P and highly associated with *BRAF* mutation and CIMP (114). If verified, recognition of these structures would require magnification colonoscopy, which is rarely available in western countries.

SSA/Ps and HPs are almost always sessile or flat. TSAs tend to be bulkier than SSA/Ps and are occasionally pedunculated, but otherwise pedunculated serrated lesions are rare. SSA/Ps are less discrete than adenomas with borders that can be difficult to define. Large SSA/P may develop folds and “wrinkle” when snared, a feature that gives them the appearance of redundant mucosa. It is likely that factors that affect colonoscopy quality and detection of flat and depressed colon neoplasms, such as bowel preparation (115–117), withdrawal time,

thoroughness of examination, polypectomy technique, and perceptual and personality attributes, will apply to SSA/Ps as well (118).

Detection rates of "serrated" lesions vary dramatically between endoscopists, indicating that these lesions are significantly under-diagnosed in clinical practice (73, 119). In one study (73), the endoscopy and pathology reports from all average risk-screening colonoscopies at an urban academic medical center over a 3-year period were reviewed. Detection of conventional adenomas varied significantly among endoscopists (from 13.5 to 38.4% ($p < 0.001$)). Detection of HPs (7.7 to 31%, $p < 0.001$) and SSA/Ps (0 to 2.2%, $p = 0.02$) also varied significantly. Similar trends were observed for the subset of conventional adenomas, HPs, and SSA/Ps that were located in the proximal colon. In another study (119) that focused on the prevalence and detection rates of serrated polyps of all subtypes located proximal to the splenic flexure, the proportion of colonoscopies with at least one proximal serrated polyp ranged from 1% to 18%, and the detection rates per colonoscopy ranged from 0.01 to 0.26. There was a strong correlation between adenoma detection rates and proximal serrated lesion detection rates. Logistic regression showed that the endoscopist was a more powerful predictor than patient age or gender for proximal serrated lesion detection. These two studies suggest that the true prevalence of serrated lesions is likely to be higher than previously reported and show that serrated lesion detection is highly variable and operator-dependent. Miss rates for serrated lesions have not been specifically measured in tandem colonoscopy studies (120), but the range of detection rates described thus far indicates that substantial numbers of endoscopists miss more than half of the serrated lesions in the proximal colon (73, 119). Recent guidelines on the technical performance of colonoscopy have recommended thresholds for adenoma detection by individual endoscopists, but have not made separate recommendations for detection rates of serrated lesions (121, 122). However, three studies suggest a strong correlation between detection of adenomas and serrated lesions by individual endoscopists (73, 119, 123).

Adjunctive imaging methods such as chromoendoscopy, electronic chromoendoscopy (narrow band imaging, etc.), and autofluorescence have generally not been investigated for their value in specifically improving the detection of serrated lesions.

Table 4 summarizes the major endoscopic and clinical features of serrated lesions.

Recommendations regarding removal of serrated lesions

We recommend complete removal of all serrated lesions, except for diminutive sigmoid or rectal lesions. Multiple diminutive (≤ 5 mm) serrated-appearing lesions in the rectum and/or sigmoid should be randomly sampled for histology, but complete resection of all diminutive rectosigmoid serrated lesions is unnecessary. Almost all serrated lesions can be excised endoscopically, and the principles of resection are similar to those governing removal of adenomas.

Three issues that can make endoscopic resection of serrated lesions difficult are shared with adenomas: size, shape and location. Large, flat lesions are challenging to remove regardless of histology. Lesions surrounding the appendiceal orifice or in the ileocecal valve orifice may not be endoscopically removable. At least one issue making complete polypectomy difficult is relatively specific to serrated lesions: identifying the border of the lesion. Although the surface structure of serrated lesions is different from normal mucosa the true edges of serrated lesions can be difficult to identify. Complete endoscopic resection is important and use of a high definition colonoscope, an electronic highlighting technique (e.g., narrow band imaging), surface dye-spraying, and/or submucosal injection of fluid containing a contrast agent (e.g., methylene blue or indocyanine green) can assist in identifying the lesion perimeter.

Serrated lesions smaller than 1 cm can be resected with or without electrocautery. For all but the tiniest lesions, cold snaring is more efficient and effective than piecemeal resection using cold forceps (124). Cold snaring should include a narrow margin of normal mucosa around the perimeter of the lesion. When electrocautery is used, inclusion of a rim of normal mucosa is not strictly necessary, but is probably safe when submucosal fluid has been injected and likely helps to ensure complete excision.

Large serrated lesions (most likely to be SSA/P) may actually be easier to snare than large adenomas. This is because an SSA/P is generally less attached to the underlying submucosa and can be drawn into the snare more easily. Submucosal injection of these lesions sometimes makes resection more rather than less difficult by preventing the mucosal wrinkling that facilitates snaring. There is no evidence that resection of large serrated lesions is associated with an increased risk of complications despite their flat profile and proximal location, and there may be a reduced incidence of post-polypectomy bleeding (71). Piecemeal resection and application of argon plasma coagulation to destroy residual tissue that cannot be snared are appropriate techniques, but of course, the endoscopic approach to large serrated lesions will depend on lesion size, shape and location, as well as patient age and comorbidities, and the experience and judgment of the endoscopist. When piecemeal technique is used for large serrated lesions, another colonoscopy at 3 to 6 months is recommended to check for completeness of excision. In challenging cases, referral to a more experienced therapeutic colonoscopist should be considered.

Surgical resection of colon containing a serrated lesion is rarely necessary (71), but is appropriate when a serrated lesion cannot be endoscopically excised. Surgical resection may also be indicated when there are numerous large serrated lesions in the proximal colon.

Serrated polyposis syndrome

Serrated polyposis syndrome (SPS) (formerly hyperplastic polyposis syndrome) is characterized by multiple serrated (typically SSA/Ps and/or HPs) colorectal polyps. Recently updated WHO criteria define the syndrome by any one of the following conditions: (1) at least five serrated polyps proximal to the sigmoid colon with two or more of these being > 10 mm; (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS or (3) > 20 serrated polyps of any size, distributed throughout the colon (125). However, this definition is arbitrary and cannot be validated without a genotype, and no definitive gene mutation has yet been identified to correlate with the phenotype.

There is substantial phenotypic diversity (125) and it is possible that several different but related conditions may be part of SPS. SPS has near equal gender distribution (126–128), with median age at diagnosis of 44 to 62 years, and range 10–90 years (126–128). Serrated lesions in SPS are sessile polyps or flat lesions. Typically, most are < 1 cm in size, and polyps > 1 cm are more often located in the proximal colon. Patients often have one or more synchronous adenomas (126–128).

SPS demonstrates hallmarks of a genetic disease, including multiple lesions, younger age of onset of lesions, family history of neoplasia, as well as restricted ethnicity in some studies (129, 130), but most cases are sporadic. The polyposis is an indication of a “methylator milieu” existing in the mucosa (131) and acquired either by inheritance or by exposure to as yet unknown environmental agents.

The exact risk of CRC in SPS is unknown. Case series have reported up to 25% to 50% rates of synchronous cancer at diagnosis (126–128, 132–138). A retrospective study found a cumulative risk of CRC of 7% at 5 years in patients under surveillance (126). These

estimates are subject to ascertainment bias, however, and the risk estimates are likely to be inflated.

Surgery is generally indicated in SPS when CRC is diagnosed or when the size and/or number of polyps makes endoscopic control not feasible. Surgery for patients with SPS should include resection of any segment with cancer and at least those segments with large polyps. Extended right hemicolectomy and subtotal colectomy are the most common operations. Annual endoscopic surveillance of any residual colon and rectum is appropriate. When long-term endoscopic management is attempted, annual colonoscopy should be performed with intent to clear the proximal colon of all serrated lesions, or all serrated lesions ≥ 5 mm in size if there are numerous diminutive lesions. The surveillance interval and/or the management strategy can be altered if subsequent examinations reveal progressive control or loss of control of the polyp burden.

Nearly half of SPS patients have a family history of CRC (128, 132), and one study reported an elevated relative risk of CRC in first-degree relatives of patients with SPS of 5.4 (139). It is recommended that screening colonoscopy be performed in first degree relatives aged ≥ 40 years, or beginning at an age 10 years younger than the age at diagnosis of the youngest affected relative. Colonoscopy is recommended at 5 year intervals, or more frequently if polyps are found.

Post-polypectomy surveillance of patients with serrated lesions

Post-polypectomy surveillance guidelines in the United States and Great Britain make recommendations for patients with adenomas based on observational studies that link baseline colonoscopy adenoma findings to the risk of an advanced adenoma at follow-up (140, 141). There are few such data available for serrated lesions (81, 93, 99, 142), but the strong association of serrated lesions with CIMP-high CRCs has led to calls for specific post-polypectomy surveillance guidelines for patients with SSA/Ps. Several authors have already made suggestions in this area (13, 17, 143–145). Recommendations for surveillance are made here, but considering the paucity of post-polypectomy observational studies addressing follow-up of serrated lesions, the recommendations reflect consensus expert opinion. The recommendations are based on the principles presented in Figure 7, and the collective approaches to serrated lesions of the panel members.

Major limitations of colonoscopy as a tool for preventing CRC include variable lesion detection rates (146–150) and variability in efficacy of polypectomy (151). When the rate of missed or persistent lesions varies significantly between endoscopists, it is difficult to make surveillance guidelines that protect all patients. While this applies to adenomas as much as to serrated lesions, cancers developing after colonoscopy are more likely to be right-sided, MSI-high and CIMP-high, suggesting that missed serrated lesions may be a major reason for the relative failure of colonoscopy to protect against right-sided colon cancers (152, 153). Thus, the first concern of colonoscopists should be effective polyp detection and resection. Because there are data describing standards for adenoma detection rate (ADR), and because ADR correlates with serrated lesion detection in some studies (73, 119), colonoscopists should know their ADR. If this is substandard (< 25% in average risk men over 50 years having screening colonoscopy, < 15% for average risk women over 50 years) (121), technique and or lesion recognition skills should be improved to bring the ADR into acceptable range. No recommendation for a detection threshold of serrated lesions is made here, but this issue is being actively studied. Available data indicate that miss rates and variability in detection are greater for serrated lesions than for adenomas (73, 119).

Figure 7 presents the conceptual framework that underlies the risk stratification scheme presented in Table 5. Much of this framework and its basis in the literature in discussed

elsewhere in this paper. As noted above, the specific recommendations for interval follow-up in Table 5 reflect consensus expert opinion rather than a substantial evidence base. As post-polypectomy surveillance studies of serrated lesions become more available, evidence based guidelines will be developed that will supersede such recommendations.

Accurate characterization of the number, size and location of lesions is dependent on the endoscopist. Accurate characterization of histology is dependent on the pathologist. This paper emphasizes the importance of effective detection and resection and also provides pathologic criteria for the distinction between HP and SSA/P. Endoscopists and pathologists should share this information and work cooperatively to improve care in their institution, but clinicians should consider use of the SSA/P recommendation when proximal serrated lesions > 1 cm in size are interpreted as HPs, as there is likely substantial variation between pathologists in this regard. Endoscopy findings may be critical for interpretation of histological findings and should be available to pathologists.

Given the paucity of observational studies after endoscopic resection of serrated lesions (81, 93, 99, 142), we sought other evidence to guide surveillance recommendations. We identified several rationales for establishing relatively aggressive surveillance recommendations (Table 5) following resection of serrated lesions pending availability of additional observational studies. First, interval cancers (cancers occurring after colonoscopy) are more likely to be right-sided, MSI-high and CIMP-high (152, 153). Given that colonoscopy is less effective in preventing proximal than distal cancers (146, 147, 154, 155), these data suggest that serrated lesions (and failure to detect serrated lesions) are an important contributor to failure of colonoscopy to prevent colorectal cancer. Second, initial studies have found that variability in detection of serrated lesions in the proximal colon is greater (73, 119) than has been reported for adenomas (149, 150), supporting a rationale for relatively close intervals to compensate for increased missing of serrated lesions. Third, there are insufficient data on the effectiveness of endoscopic resection of serrated lesions. However, the very flat shape of many SSA/Ps, combined with the indiscrete borders of these lesions, raises concerns that incomplete resection of serrated lesions may be an important clinical problem. These factors combine to create a tendency toward aggressive recommendations after resection of serrated lesions. However, aggressive post-polypectomy surveillance is acknowledged as a poor replacement for endoscopists who are well trained in lesion recognition, examine the colon carefully, and resect pre-cancerous lesions completely.

Recommendations for post-polypectomy surveillance of patients with serrated lesions are subject to modification based on physician judgment. If multiple types of serrated lesions are present, the shortest recommended interval should be considered. Subsequent colonoscopies that identify no lesions or serrated lesions that are fewer in number, smaller, etc., can be followed by expansion of the interval. When synchronous serrated lesions and conventional adenomas are present, opting for the shorter interval that would be appropriate based on either type of lesion is acceptable or further shortening the interval based on number of lesions of both types may be appropriate.

Summary

Serrated lesions should be classified as hyperplastic polyp, sessile serrated adenoma/polyp (SSA/P) with or without cytological dysplasia, or traditional serrated adenoma (TSA). SSA/P is located primarily in the proximal colon, and is an important precursor of colorectal cancers. Cancers arising through the serrated pathway are typically CIMP-high, demonstrate *BRAF* mutations, and may demonstrate MSI.

It has been recently proposed that the colorectum biologically represents a continuum, rather than a two-sided tube with a sharp border at splenic flexure (47, 156). Evidence suggests

that cecum may be a separate place from the other colorectal subsites, with a high frequency of *KRAS* mutations in cecal cancers (47). Future research on serrated and other precursor lesions needs more collaboration and adequate sample sizes to address biological, microbial, and microenvironmental heterogeneity in detailed colorectal subsites.

SSA/Ps are flat or sessile with a distinct endoscopic appearance that is often quite subtle. Effective colonoscopy requires understanding of the typical appearance of serrated lesions, followed by accurate identification of these lesions. All serrated lesions proximal to the sigmoid and rectosigmoid lesions > 5mm in size should be fully resected.

Recommendations for colonoscopy surveillance intervals must currently be based on features of serrated lesions that are associated with advanced neoplasia including synchronous and metachronous colorectal cancer. These features include proximal colon location of serrated lesions, increasing number and larger size of serrated lesions, and SSA/P or TSA histology.

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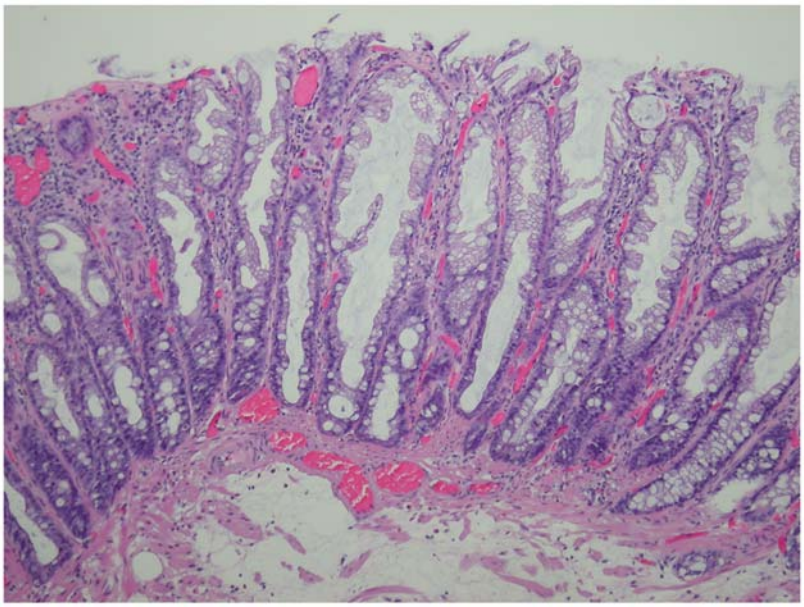
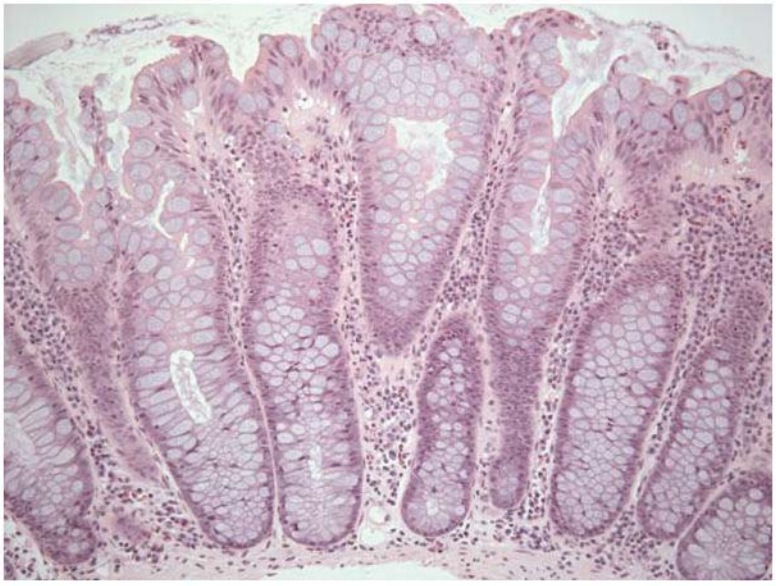




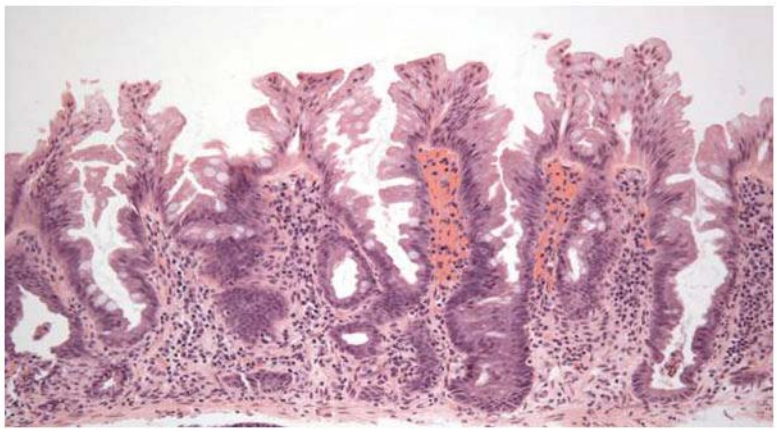


Figure 1.
Photomicrographs of hyperplastic polyps. (a) Microvesicular hyperplastic polyp (MVHP). The crypts and surface epithelium show a luminal serrated or saw-toothed contour more prominent in the upper levels of the crypts than at the base. The epithelial layer is composed of cells with goblet cell differentiation and others with microvesicular cytoplasmic mucin. (b) Goblet cell hyperplastic polyp. In contrast to MVHP, this polyp shows a much less pronounced serrated or saw-toothed luminal epithelial growth pattern and shows a preponderance of goblet cells and an absence of cells with microvesicular mucin. The crypts are straight, linear, and without architectural distortion. (c) Mucin poor hyperplastic polyp. The overall configuration of this polyp is similar to the microvesicular hyperplastic polyp but the cells are mucin depleted. The nuclei also are more hyperchromatic than the MVHP.

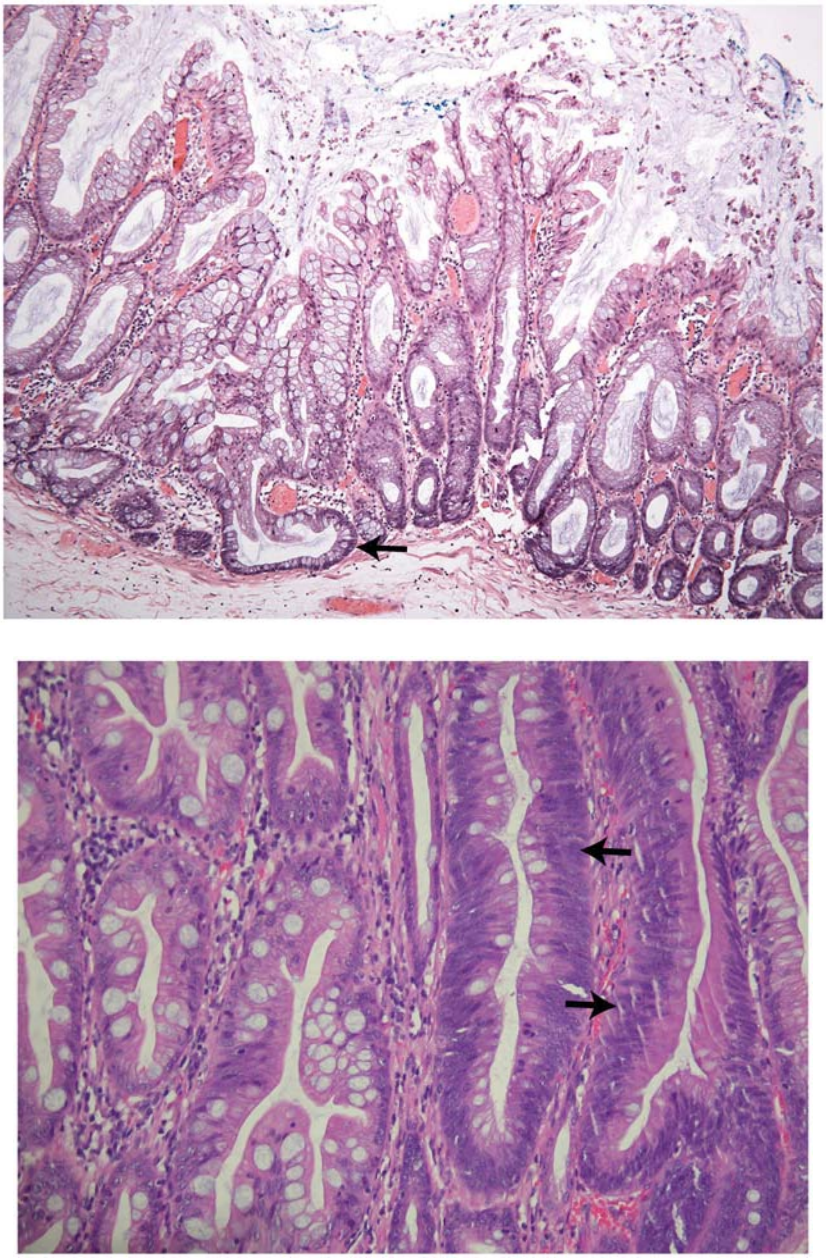


Figure 2.
Photomicrograph of sessile serrated adenoma/polyps. (a) A sessile serrated adenoma/polyp showing a hyperserrated luminal epithelial growth pattern more pronounced that in microvesicular hyperplastic polyps. In addition, the crypts show luminal dilation towards the bases of the crypts, some crypts show horizontal growth along the long axis of the muscularis mucosa (arrow). Goblet cells are present at all levels of the crypts, some of which are dystrophic. Mitotic figures are easily recognized, and located predominantly in the basal aspects of the crypts. (b) Sessile serrated adenoma/polyp with cytological dysplasia. The portion of the polyp without cytological dysplasia on the left shows cells with uniform nuclei without pseudostratification. The cytologically dysplastic portion on the right (arrows) show hyperchromatic pseudostratified nuclei with numerous mitoses.

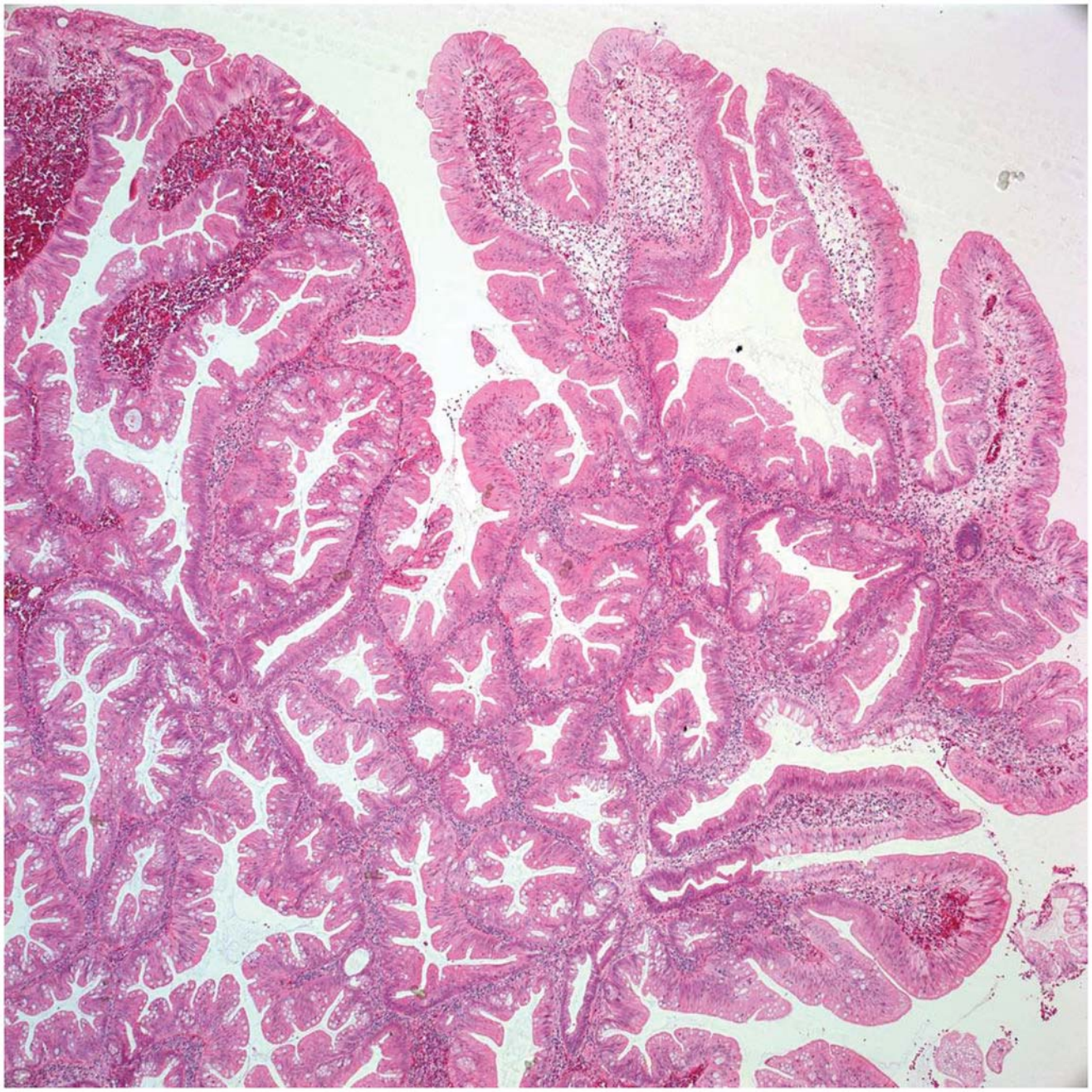


Figure 3.
Traditional serrated adenoma. This polyp is composed of villiform projections of hypereosinophilic cells with small oval-shaped nuclei oriented basally along the basement membrane. The cells are growing in a hyperserrated luminal contour. Multiple ectopic crypts are present. These are composed of crypts oriented perpendicular to the long axis of the villi. Overall, goblet cells are decreased in number.

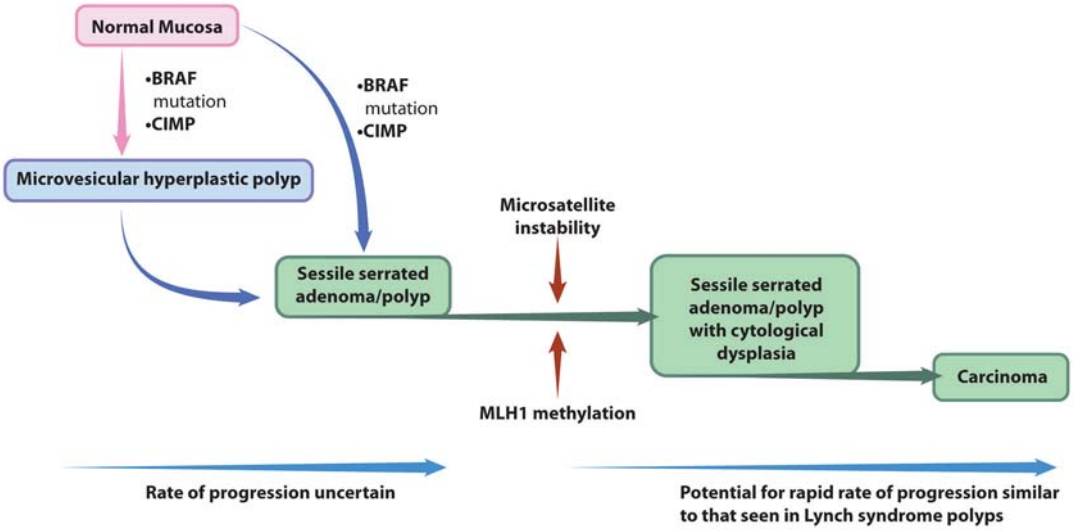


Figure 4.
A schematic representation of the putative development of CIMP-high CRCs with microsatellite instability through a serrated pathway via methylation of the *MLH1* gene.

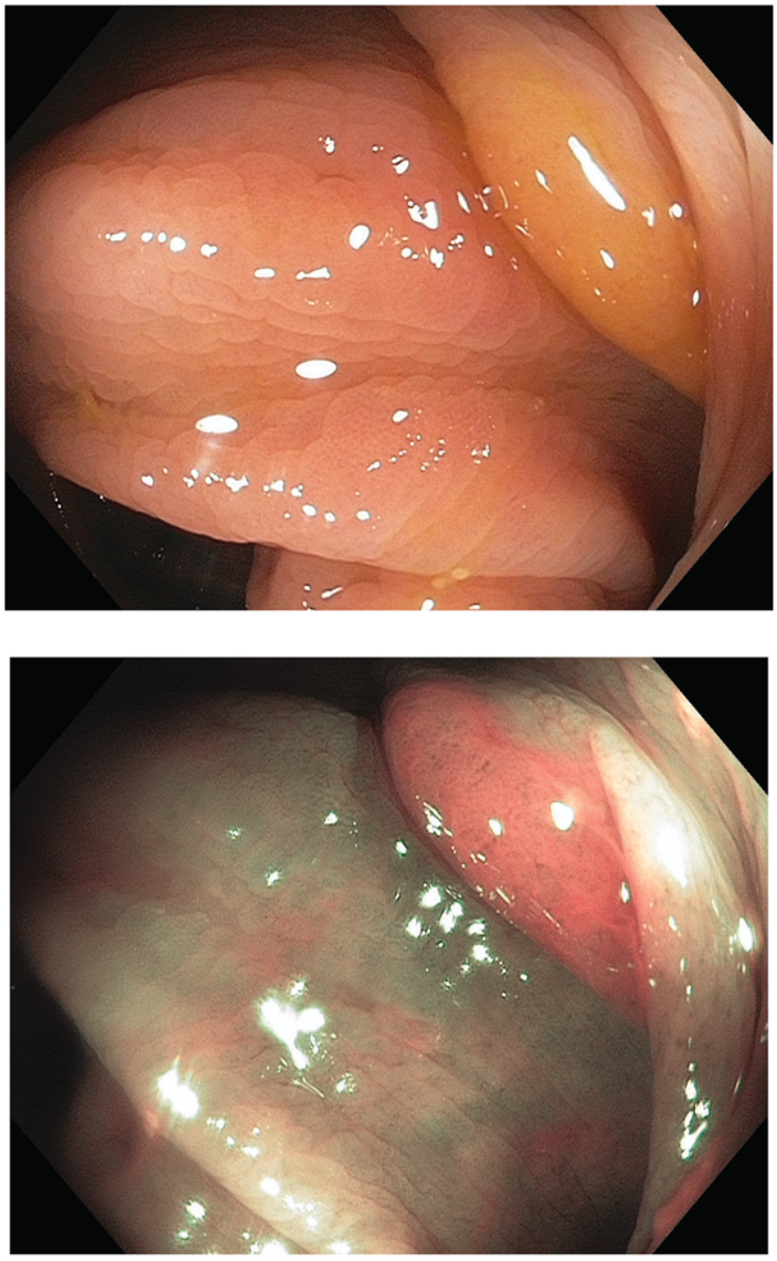
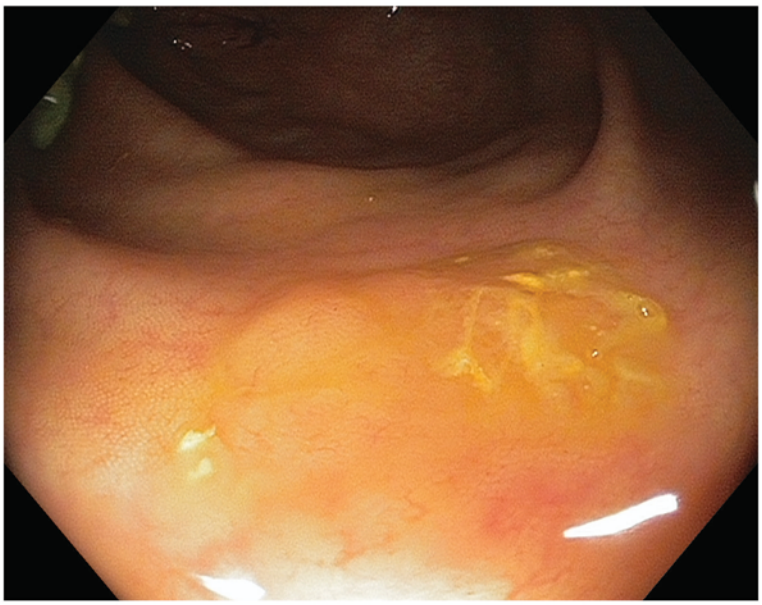
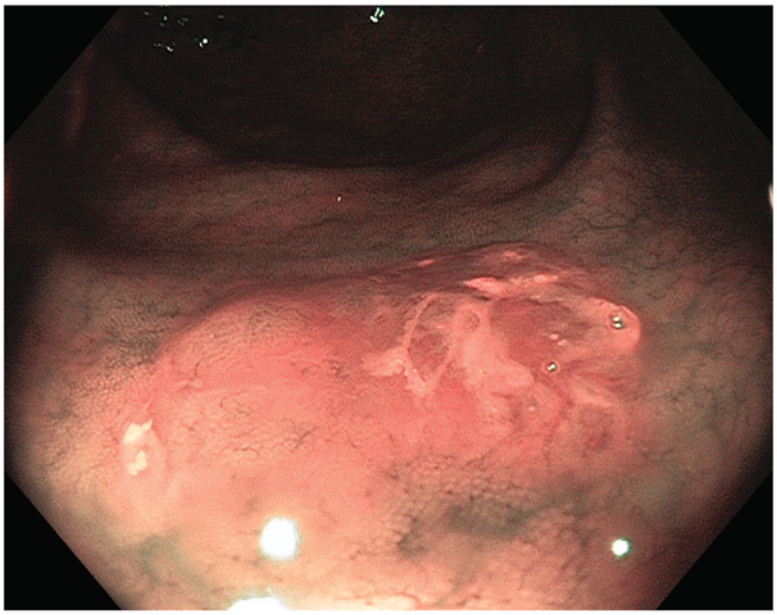
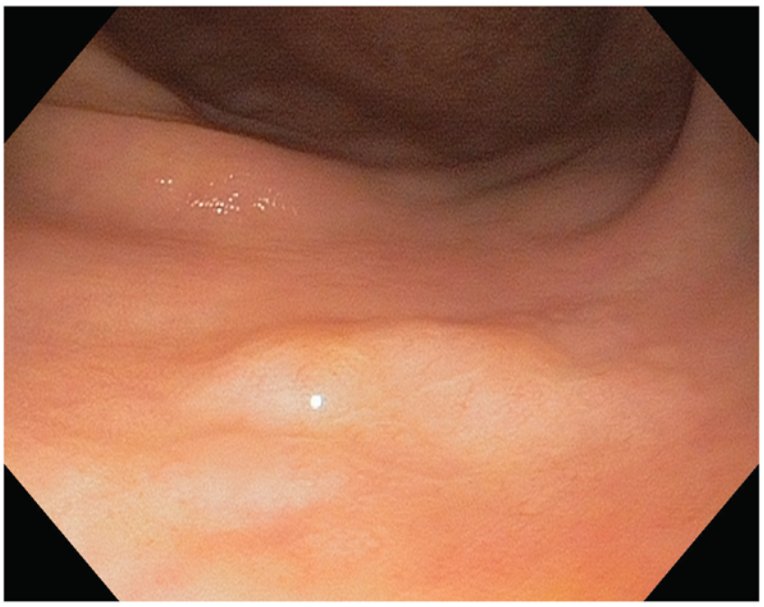
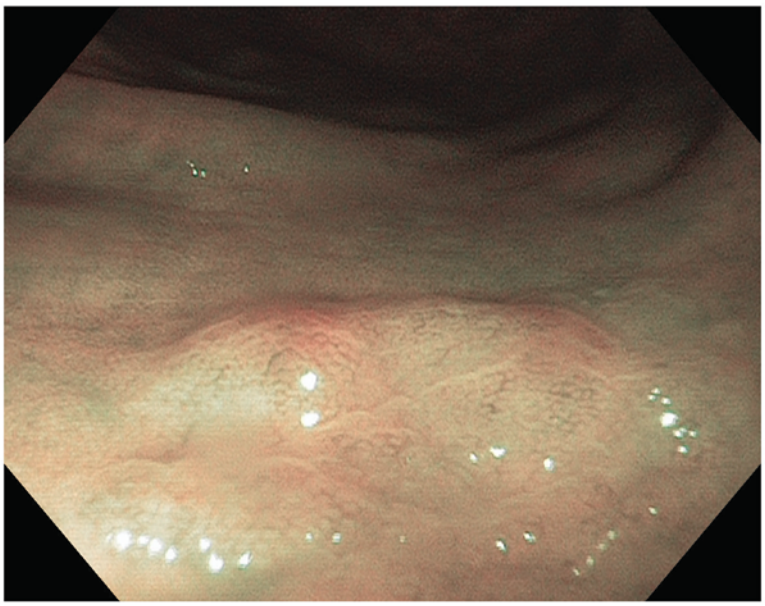


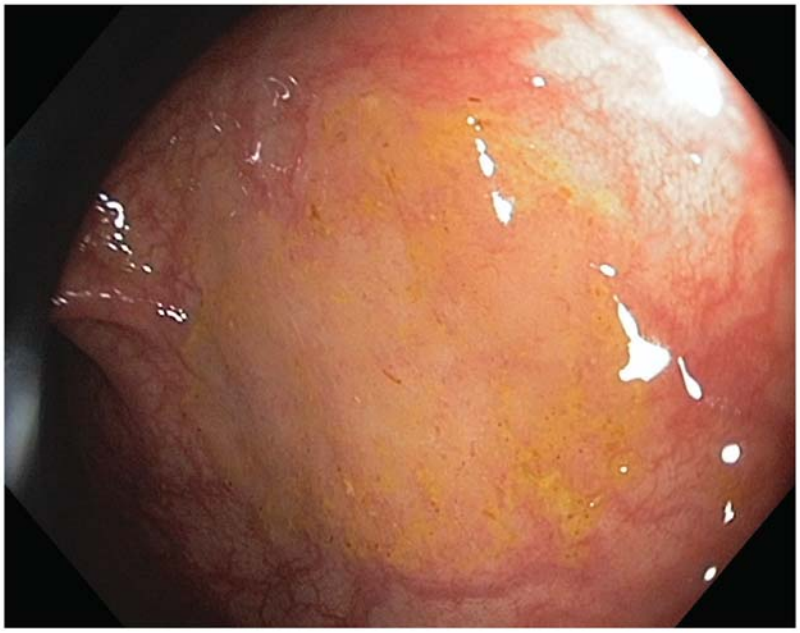
Figure 5.
Both sessile serrated adenoma/polyps and hyperplastic polyps in the proximal colon may demonstrate a “mucus cap,” which may be yellow, green or rust-colored in white light (a) and red in narrow-band imaging (b).

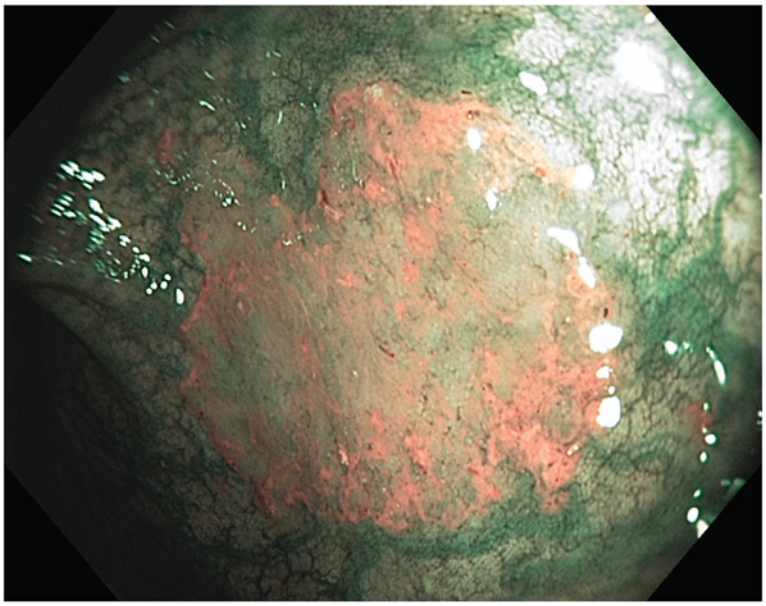


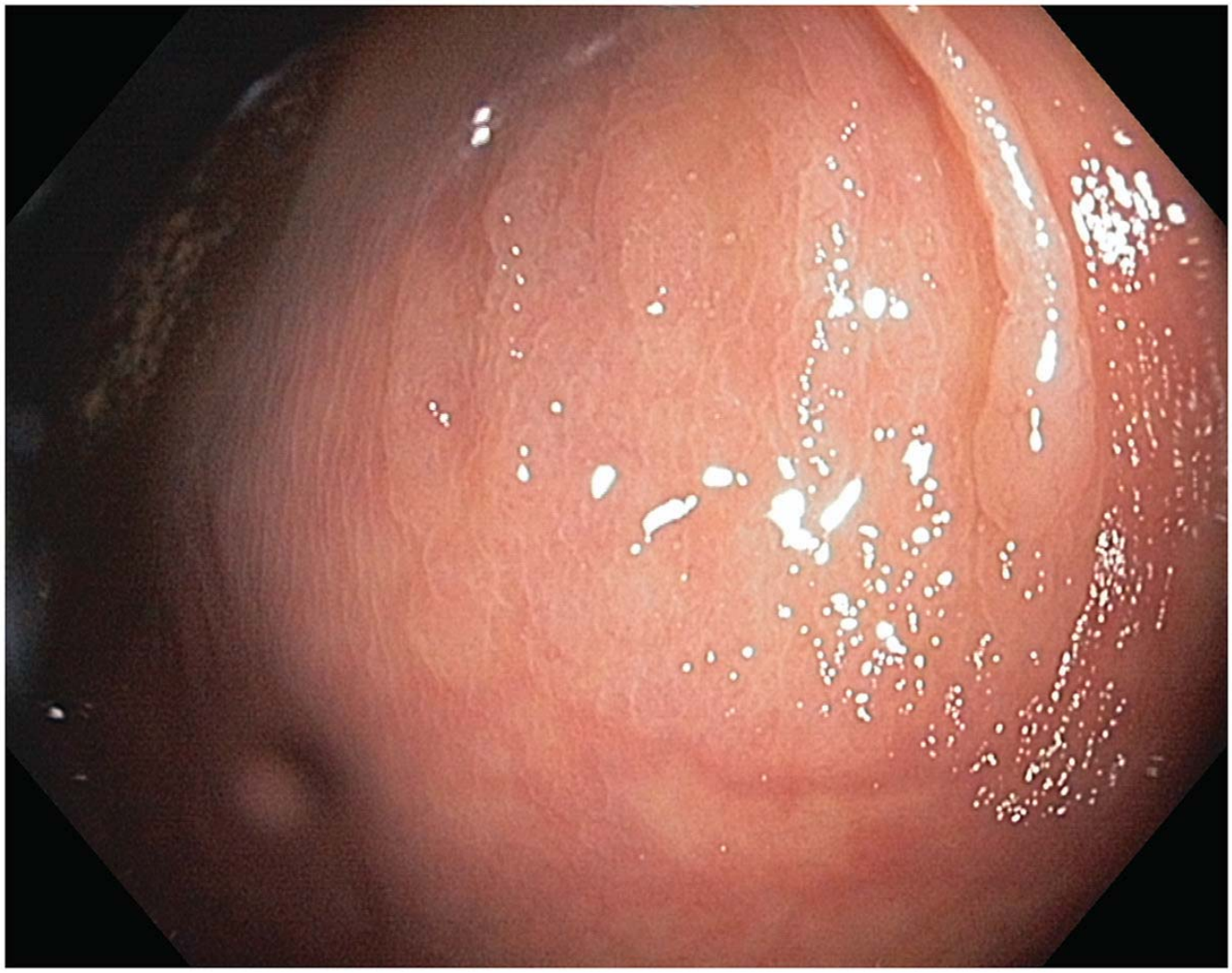












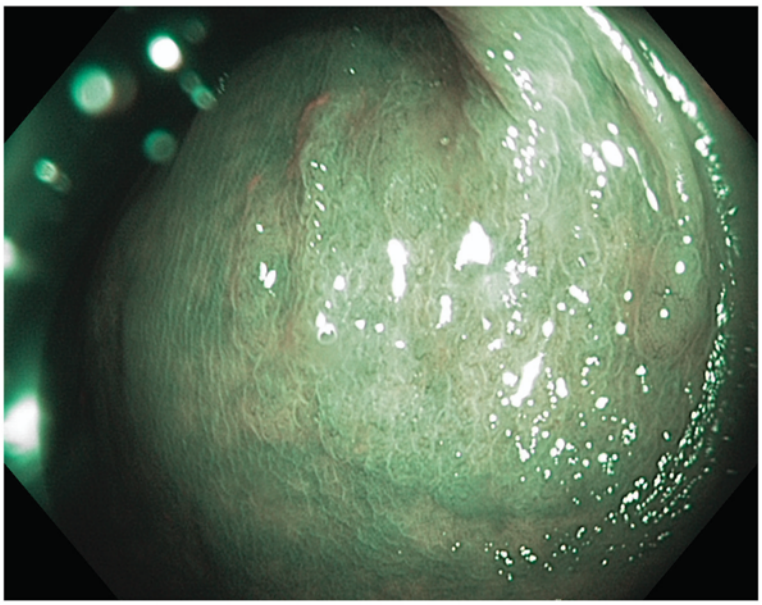


Figure 6.

Typical serrated lesions in the proximal colon. a–d. A sessile serrated adenoma/polyp in the cecum. Note the adherent mucus in white light (a) and with narrow-band imaging (b). After removal of the cap by washing the characteristics surface features are seen in white light (c) and narrow-band imaging (d), including indistinct edges, color similar to the surrounding normal mucosa, and a paucity of blood vessels. e–h. A flat sessile serrated adenoma/polyp in the transverse colon, with the mucus cap in white light (e) and narrow-band imaging (f) and with the cap washed off in white light (g) and blue light (h). Note the subtlety of the lesion after the cap is washed off.

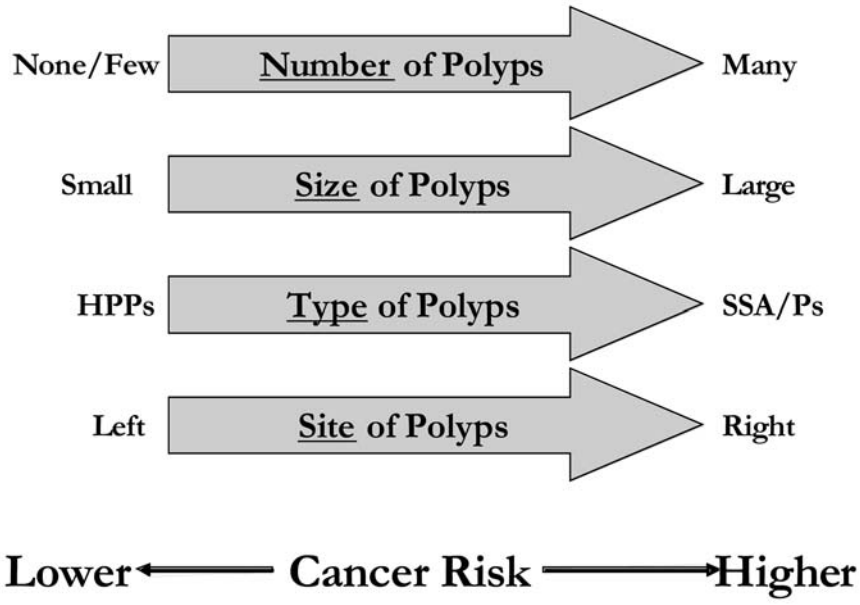


Figure 7.
The risk of developing colorectal cancers through the serrated pathway parallels the number, size, type, and anatomic distribution of the serrated polyps.

Table 1

Pathologic classification of serrated colorectal polyps recommended by the World Health Organization

- Hyperplastic polyp
- Sessile serrated adenoma/polyp *
  - With or without cytological dysplasia
- Traditional serrated adenoma

The terms

*"Sessile serrated adenoma" and "sessile serrated polyp" are considered synonymous

Table 2

Key conclusions and recommendations of the consensus group *

Pathology	
1	Serrated lesions of the colorectum should be classified histologically as hyperplastic polyp (HP), sessile serrated adenoma/polyp (SSA/P) with or without cytologic dysplasia, or traditional serrated adenoma (TSA). Exceptions and subcategories are discussed in the text. Clinicians and pathologists within institutions should work collaboratively to achieve a common usage and understanding of terminology of serrated lesions.
2	SSA/P and TSA are pre-cancerous lesions. SSA/P is the principal precursor of hypermethylated colorectal cancers (cancers with the CpG Island Methylator Phenotype – CIMP). This pathway occurs primarily in the proximal colon.
3	SSA/P is distinguished from HP pathologically by findings of crypt distortion, particularly in the crypt base, in SSA/P. We recommend that a single unequivocal architecturally distorted, dilated, and/or horizontally branched crypt, particularly if it is associated with inverted maturation, is sufficient for a diagnosis of SSA/P. Most large serrated lesions in the proximal colon are SSA/Ps.
4	SSA/P with cytological dysplasia is a more advanced lesion in the progression to cancer compared to SSA/P without cytological dysplasia.
Endoscopy	
5	SSA/P and hyperplastic polyps in the proximal colon have a distinct endoscopic appearance, which includes a “mucus cap”, color usually similar to normal mucosa, and indistinct edges. All colonoscopists should be able to recognize serrated lesions.
6	Detection of proximal colon serrated lesions by individual endoscopists is highly correlated with adenoma detection. Pending development of specific detection targets for proximal colon serrated lesions, endoscopists should measure their adenoma detection rates as a check on adequate detection of serrated lesions.
7	All serrated lesions proximal to the sigmoid colon should be fully resected during colonoscopy. All serrated lesions in the rectosigmoid colon > 5 mm in size should be fully resected.
Surveillance	
8	Serrated polyposis is defined by the World Health Organization (see text for details). Patients with serrated polyposis require close endoscopic follow-up with control of polyp burden by endoscopy or by surgical resection if the number, size or location of serrated polyps precludes endoscopic resection or if a cancer is diagnosed.
9	First degree relatives of patients with SPS should undergo colonoscopy at age 40 or 10 years before the age at diagnosis of SPS. Colonoscopy should be at 5 year intervals or more often if polyps are found.
10	There are few longitudinal observational studies after removal of serrated lesions on which recommendations for post-polypectomy surveillance can be based. Recommendations are mostly based on features of serrated lesions for which there is evidence of an association with increased risk of cancer or advanced neoplasms, including: proximal colon location, large size, increasing number, and histologic features including SSA/P histology (see text and Table 5, Figure 7 for details).

* Clinical recommendations made here are considered strong by the panel, but are supported by low quality or very low quality evidence, and are likely to change when higher quality evidence becomes available.

Table 3

Molecular features of colorectal polyps and cancers. Conventional adenomas have a pattern of molecular features similar to CIN CRCs; SSA/Ps have features similar to CIMP-high CRCs.

	CIMP-high	*MLH1* methylation	MSI	*BRAF* mutation	*KRAS* mutation
Conventional adenoma	+	−	−	−	++
CIN CRC	+/−	−	−	+/−	++
Lynch CRC	−	−	+++	−	++
HP[a]	+	−	−	+	+
SSA/P	+++	−	−	+++	−
SSA/P with cytological dysplasia	+++	++	++	+++	−
CIMP-high CRC	+++[b]	+++	+++	+++	−
TSA	++	−	−	+[c]	+[c]

CRC: colorectal cancer; CIN: chromosomal instability pathway; HP: hyperplastic polyp; SSA/P: sessile serrated adenoma/polyp; CIMP; CpG island methylator phenotype; TSA: traditional serrated adenoma; MSI: microsatellite instability.

−: not typically present; +/− may be present, but infrequent with an overall inverse association between a lesion and a molecular feature; + present to a limited extent or in some subsets but not others; ++: generally present; +++: extensively present.

[a] microvesicular HPs are commonly CIMP-high and have *BRAF* mutations and goblet cell HPs commonly have *KRAS* mutations (see supplemental material for details of this histologic distinction);

[b] by definition;

[c] TSA may have *BRAF* or *KRAS* mutations or neither.

Table 4

Clinical features of serrated lesions

	Shape	Mean Size	Prevalence	Location	Pre-cancerous
HP	flat, sessile	small, often ≤ 5mm	very common	left colon	no
SSA/P	flat, sessile	larger * than HP	Common **	right colon	yes
TSA	sessile, pedunculated	larger than HP	rare	left colon	yes

HP: hyperplastic polyp; SSA/P: sessile serrated adenoma/polyp; TSA: traditional serrated adenoma

* SSA/P may be < 1cm in size, but the mean size of SSA/P is larger than the mean size of HP. Most serrated lesions ≥ 1cm in size are SSA/P

** Mean detected prevalence rates ≤ 2%

Table 5

Consensus opinion surveillance intervals after endoscopic resection of serrated lesions[+]

Histology	Size	Number	Location	Interval in years
HP	< 10 mm	any number[*]	rectosigmoid	10[***]
HP	≤ 5 mm	≤ 3	proximal to sigmoid	10
HP	any	≥ 4	proximal to sigmoid	5
HP	> 5 mm	≥ 1	proximal to sigmoid	5
SSA/P or TSA	< 10 mm	< 3	any	5
SSA/P or TSA	≥ 10 mm	1	any	3
SSA/P or TSA	< 10 mm	≥ 3	any	3
SSA/P	≥ 10 mm	≥ 2	any	1–3[***]
SSA/P w/dysplasia	any	any		1–3[****]

[+] The interval recommendations presented here represent consensus opinion based on low quality or very low quality evidence. They are likely to change as higher quality evidence becomes available, and alternatives may be equally reasonable.

[*] Patients with > 20 HPs in the rectosigmoid meet the World Health Organization definition of serrated polyposis if there are additional serrated lesions proximal to the sigmoid.

[**] Some panel members follow a policy of 5 years if there are multiple HPs 6–9mm in size in the rectosigmoid.

[***] Patients with 2 or more serrated polyps ≥ 10 mm in the proximal colon meet the World Health Organization criteria for serrated polyposis if 3 additional serrated lesions of any size are proximal to the sigmoid are identified.

[****] SSA/P with cytological dysplasia is a more advanced lesion than SSA/P. Depending on the size of the lesion, the confidence in complete endoscopic resection, and other associated lesions, intervals shorter than 3 years may be appropriate.

[+] Grade: see definitions of grade recommendations in Table 3.

Note 1: Patients with both significant serrated polyp findings and concurrent adenomas may be at a more advanced stage in the progression toward cancer. Closer follow up may be indicated in some cases based on clinical judgment.

Note 2: In general, these recommendations for surveillance are for the first follow up. For findings with short follow up recommendations, a longer subsequent follow up interval may be appropriately applied when a follow up exam shows improvement in findings, i.e. reductions in the number, size, and/or histologic severity of lesions.

Note 3: Because of interobserver variation in the pathologic differentiation of HP from SSA/P, proximal colon serrated lesions > 10 mm in size that are designated HP may be considered to be SSA/P by clinicians.