

Serrated Polyps, Part 2: Their Mechanisms and Management **Ryan C. Romano, DO**

In the prelude to this article (Serrated Polyps Part I: Their Confusing History) we discussed the evolution of colorectal serrated polyp classification, a group that comprises hyperplastic polyps (HP), sessile serrated polyps/sessile serrated adenomas (SSP/SSA), and traditional serrated adenomas (TSA). Classification of these lesions is complicated by overlap of morphologic features and significant diagnostic interobserver variability.¹ These features include prominent serration of the crypt epithelium and varying degrees of nuclear atypia and dysplasia (rare in HP, variable in SSA/SSP, and common in TSA).²⁻⁶

When serrated polyps progress to malignancy, they do so via a novel molecular pathway, and this pathway may be attributed to up to 30% of sporadic colorectal cancers and up to 15% to 20% of all colorectal cancers.^{3,5,7} The CpG-island-methylation-phenotype (CIMP), as this pathway is known, refers to hypermethylation of dense clusters of cytosine-guanine dinucleotides, CpG islands, which are present in promoter regions of approximately half of all genes.^{3,8} Aberrant hypermethylation leads to silencing of genes that encode tumor suppressor genes and mismatch repair genes, leading to microsatellite instability.^{3,5} This pathway may promote earlier progression from SSA to carcinoma when compared to the traditional adenomacarcinoma timeline, making surveillance intervals a critical metric to reevaluate.⁵ In addition, the oncogene BRAF is mutated in approximately 80% of serrated adenomas. This is often a single, activating point mutation (V600E) leading to constitutive signaling of the mitogen-activated protein kinase (MAPK) pathway, resulting in cell proliferation and survival. To contrast, BRAF mutations are rare in conventional adenomas.³

Risk factors for the development of serrated polyps appear to be the same as those for development of other colonic polyps and include advancing age, smoking, increased body mass index, and inflammatory bowel disease, among others.⁹⁻¹² Clinical diagnosis and detection of serrated polyps may be difficult using CT colonography or traditional endoscopy, as the lesions are often flat, pale with minimal vascular changes of the mucosa, and may be masked by prominent mucous.³ Chromoendoscopy may significantly improve detection.^{3,13} Fecal occult blood testing is of little value given that serrated polyps are less likely to bleed than adenomatous polyps.¹⁴ Novel biomarkers

such as SDC2, which detect DNA hypermethylation, show promise for noninvasive detection of colorectal cancer, though further investigation is needed to validate its use in screening, to clarify expression profiles of SDC2 in various polyps, and to determine if its expression is indeed exclusive to colorectal cancer.¹⁵

All but the most diminutive distal hyperplastic polyps should be completely removed whenever possible.³ Patients found to have a nondysplastic sessile serrated polyp ≤ 10 mm should undergo repeat screening colonoscopy in five years. A three-year surveillance interval is assigned to SSAs ≥ 10 mm, an SSA of any size with dysplasia, and TSAs. Patients with serrated polyposis syndrome should be screened annually.¹⁶

Inconsistent or confusing terminology, along with the lack of clear histologic criteria for diagnosis, has led to frequent misclassification of serrated polyps, severely impacting our ability to accurately study the epidemiological, clinical, and pathological characteristics of these lesions. As a result, little is known about the true risk of progression to carcinoma, creating a challenge for clinicians and pathologists in formulating proper management strategies. Detailed molecular profiling and the establishment of standardized diagnostic criteria will go a long way in helping to better understand the behavior of this group of polyps.^{3,5} Serrated polyps are but one example highlighting the importance of clinicopathologic correlation and communication between pathologists and clinicians.

Table 1

	Size	Endoscopy	Histology	Predominant Location	Cancer Risk	Predominant Mutations	Management
Hyperplastic Polyps * Traditionally considered nonneoplastic	<0.5 cm	Small sessile nodules, flatten on insufflation	Elongated crypts; serrated architecture top half of crypt; small uniform basally oriented nuclei; no atypia or dysplasia	Distal Colon	Minimal	Universal: BCL2/BAX; loss of heterozygosity of chromosome 1p and APC Microvesicular Subtype: DNA methylation, BRAF Goblet Cell Subtype: KRAS Mucin-poor Subtype: Poorly understood	Removal: Not indicated Surveillance 10 yrs.

	Size	Endoscopy	Histology	Predominant Location	Cancer Risk	Predominant Mutations	Management
Sessile Serrated Polyps/Sessile Serrated Adenomas	>0.5 cm	Smooth surface; often covered with mucus	Hyperserration in lower third of crypts; crypt dilation; flattening of crypts (T- and L-shaped) along muscularis mucosae	Proximal colon	Limited data, but appears increased	DNA hypermethylation (CIMP) BRAF activation due to point mutation (V600E)	Complete endoscopic removal Surveillance <10mm, no dysplasia: 5 yrs. >10 mm or dysplasia: 3 yrs.
Traditional Serrated Adenomas	>0.5 cm	Variable; may be sessile, pedunculated, or flat/carpet-like	Prominent crypt serration; Confluent pink, eosinophilic cytoplasm in epithelium; papillary or villiform growth pattern; intra-epithelial neoplasia by definition (90% low-grade)	Distal colon	Limited data, but appears increased	DNA hypermethylation (CIMP); BRAF activation	Complete endoscopic removal Surveillance 3 years

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