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Serrated Polyps, Part 1: Their Confusing History
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Historically, colorectal polyps have been classified into two major categories, nonneoplastic and neoplastic, each group having its own signature lesion. Traditionally, hyperplastic polyps nearly exclusively comprosed the nonneoplastic group.[1] The majority of remaining polyps was classified as adenomas and were generally thought to be the exclusive precursors to colorectal cancer due to an increased risk of malignant progression when exhibiting villous histology or high-grade dysplasia, or when greater than 1 cm in diameter.[2,3] This dichotomous classification system existed for decades, though not without controversy.

Hyperplastic polyps (HPs) were traditionally considered a single entity despite variations in morphologic appearance. They typically demonstrate a prominent serrated or saw-toothed appearance of the basal half of the crypts with rare to absent nuclear atypia or stratification, and normal surface maturation.[1,4,5] The serrated histologic architecture is a product of decreased apoptosis of epithelial cells, leading to increased numbers of retained cells and the characteristic serrated appearance.[5,6] HPs characteristically are less than 5 mm in size, located in the rectosigmoid and left colon, and carry minimal risk of progression to malignancy. There is a suggested slight increased risk of malignant potential when located in the proximal colon or when larger than 10 mm.[6-8] Endoscopically, they are often flat to slightly elevated and pale, and they generally flatten upon insufflation of air.[5,6] In general, HPs are considered microsatellite stable and have no consistent immunohistochemical staining pattern. Though some distinct architectural patterns have been suggested, routine subclassifcation of HPs has not been universally adopted in clinical or pathologic practice.[6]

Traditional serrated adenoma (TSA) is another type of serrated polyp. Originally classified in 1990, TSAs are predominantly left-sided lesions that show prominent serration and traditional adenomatous dysplasia consisting of nuclear enlargement, hyperchromasia, and stratification. TSAs carry a higher risk of progression to carcinoma than traditional adenomas. [6,9]

The controversy over this dichotomous (hyperplastic polyp and adenoma) classification was born out of reports beginning in the 1970s linking adenocarcinoma with seemingly innocuous hyperplastic polyps.[10-12] In 1996 Torlakovic and Snover published the landmark paper that served as the catalyst for further investigation; it described cases of adenocarcinoma that arose out of polyps in patients with hyperplastic polyposis syndrome.[13] The polyps of these patients had a unique morphology akin to that of TSAs; however, as compared to the TSAs, the polyps described in this manuscript exhibited less traditional cytologic adenomatous atypia and were more likely to be sessile.[13] Detailed analysis of these "hybrid" lesions has given rise to a distinct polyp known as the sessile serrated adenoma (SSA).[2,9,13] SSAs characteristically exhibit dilated, branching crypts that are often flattened near the base along the muscularis mucosae, sometimes described as a "boot," or T- and L-shaped.[4,6] Hyperserration of the crypt epithelium is also prominent in the lower third of the crypts. Immunohistochemical profiles have been examined, but they are much too inconsistent to be used routinely in diagnosis.

Collectively, the family of serrated polyps includes hyperplastic polyps, traditional serrated adenomas, sessile serrated adenomas, which are synonymous with sessile serrated polyps (SSP), and mixed polyps that have features of conventional adenomas and serrated polyps.[2,5,14] One can see how terminology might hamper appropriate classification of these lesions and effective communication between pathologists and clinicians. In fact, one author describes these lesions in this manner: "A serrated (saw-toothed) architecture is the common morphologic denominator of a group of polypoid bowel lesions that have gained a lot of attention lately and which have generated a still evolving terminology which at this moment seems hopelessly confusing**."**[15] The distinction of these lesions from one another is based primarily on histologic features identified microscopically, by endoscopic appearance, genetic mutations, and clinical behavior.[6,15] Unfortunately, there is significant overlap of morphologic features and considerable interobserver variability in classification of these lesions, making it difficult to accurately assign epidemiological and molecular data, as well as make appropriate recommendations for clinical management.[4,16-18]

In our follow-on article, we will examine the family of serrated polyps in more detail, including the unique molecular pathway that helps define these lesions.

Table 1

	Size	Endoscopy	Histology	Predominant Location	Cancer Risk	Predominant Mutations	Management
Hyperplastic Polyps * Traditionally considered nonneoplastic	<0.5 cm	Small sessile nodules, flattened 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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