

ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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Serrated Polyps in the Colon



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G&H What are the various types of precancerous colonic polyps?

DR There are 2 major classes of precancerous polyps in the colon. One class is the conventional adenomas, all of which are dysplastic. (The dysplasia should be classified as low or high grade.) Conventional adenomas are also classified as tubular or villous or, if there is a mixture of tubular and villous elements, as tubulovillous. This class of polyps is the precursor of colorectal cancer in 2 of the 3 major molecular pathways: the chromosomal instability pathway, which accounts for approximately 65% to 70% of all colorectal cancers, and the Lynch pathway, which accounts for approximately 3% of colorectal cancers.

The other class of precancerous polyps in the colon is a subset of the serrated lesions, which is currently understood to be the precursor of the remainder of colorectal cancers. Unlike conventional adenomas, which are uniformly dysplastic, the vast majority of serrated lesions contain no dysplasia. The serrated class includes the hyperplastic polyps, which are not considered precancerous; sessile serrated polyps (also called sessile serrated adenomas; Figures 1 and 2); and traditional serrated adenomas, which are quite rare and often mistaken by pathologists for conventional adenomas.

G&H Can sessile serrated polyps be differentiated from hyperplastic polyps based on endoscopic inspection?

DR It is difficult to reliably differentiate sessile serrated polyps from hyperplastic polyps during endoscopy. There are, however, several clues that can help an endoscopist estimate whether a polyp is a sessile serrated polyp as opposed to a hyperplastic polyp. Sessile serrated polyps are larger on average and more often located in the proximal colon. Sessile serrated polyps have a more irregular surface, a pattern to the surface that has been called “cloudlike,” and indistinct edges compared with hyperplastic polyps. Sessile serrated polyps also have large open pits on the surface (type O pits) when viewed with magnification. These pits appear as large dark spots with high-definition, standard-magnification colonoscopes. Although endoscopic differentiation of sessile serrated polyps from hyperplastic polyps is challenging, endoscopic differentiation of serrated lesions as a class from conventional adenomas as a class is straightforward.

G&H Can pathologists accurately differentiate sessile serrated polyps from hyperplastic polyps?

DR There is large interobserver variation among pathologists in this area. The main histologic feature that distinguishes sessile serrated polyps is dilation and/or lateral growth of the crypts, usually at the base of the crypts. Only 1 crypt needs to be abnormal to make a serrated lesion a sessile serrated polyp and not a hyperplastic polyp. Understandably, when the number of affected crypts is small



Figure 1. A mostly flat sessile serrated polyp in the right colon. Note the similar color to the adjacent normal colon, the paucity of blood vessels on the surface of the lesion, and the accumulation of yellow “debris” at the edges.

and the crypt changes are minor, there will be reduced agreement among pathologists. This creates uncertainty among endoscopists in clinical practice about whether they should accept pathologists’ interpretations of lesions in the serrated class. It also creates difficulty in clinical trials attempting to establish endoscopic criteria for whether a polyp is a sessile serrated polyp or a hyperplastic polyp because there is no reliable gold standard in pathology; even expert pathologists have levels of agreement that are at best moderate and at worst quite poor for differentiating sessile serrated polyps from hyperplastic polyps. There also appear to be pathologists who are either not informed about sessile serrated polyps or who do not acknowledge the concept of sessile serrated polyps as a distinct entity from hyperplastic polyps. Thus, in clinical practice, endoscopists may encounter pathologists who never or very seldom use the term *sessile serrated polyp* or *sessile serrated adenoma* in their reports. There are some endoscopists, myself included, who believe that any lesion in the serrated class that is larger than 1 cm in size and has been removed from the proximal colon should be treated as a sessile serrated polyp, even if a pathologist has called the lesion hyperplastic. This policy could change as endoscopic criteria for sessile serrated polyps become better defined.

G&H Why is the identification of serrated polyps important? What is their relationship to the development of colorectal cancer?

DR Sessile serrated polyps have a high prevalence of hypermethylation and mutations in the *BRAF* oncogene. These features are shared with a group of colorectal cancers that are hypermethylated. Sessile serrated polyps are



Figure 2. A sessile serrated polyp in the right colon. Note the prominent “mucus cap.”

common in the proximal colon, the same location where hypermethylated cancers are more common. Traditional serrated adenomas are relatively rare and predominantly left-sided, and their molecular profile is not well characterized. Therefore, sessile serrated polyps appear to be the predominant precancerous lesions in the serrated class.

Sessile serrated polyps are, on average, more difficult to detect than conventional adenomas. This is likely because the color of the lesions is nearly always similar to that of the surrounding mucosa, their profile is always flat or sessile, and the edges of these polyps are frequently difficult to define. Patients who develop cancer after colonoscopy are more likely to have hypermethylated cancers than are patients whose cancers are diagnosed at an initial colonoscopy. Thus, the detection of sessile serrated polyps is an important goal during colonoscopy.

A commonly discussed issue is whether cancers developing through a serrated pathway transition more quickly through a polyp–cancer sequence than occurs in the conventional adenoma–cancer sequence. Some evidence suggests that the sessile serrated polyp-to-cancer sequence takes 10 to 20 years, the same time frame generally accepted for the conventional adenoma-to-cancer sequence. However, approximately half of the cancers in the serrated pathway have microsatellite instability. In serrated lesions, microsatellite instability is caused by epigenetic inactivation of the *MLH1* gene. This inactivation is the result of methylation of the promoter region of *MLH1*. Microsatellite instability is more common in sessile serrated polyps with cytologic dysplasia, which appear histologically to be a mixture of sessile serrated polyps and conventional adenomas. The portion of the lesion that looks like a conventional adenoma is the section demonstrated by microdissection to contain microsatellite instability. Microsatellite instability is generally associated with

the potential for rapid transition to cancer. Therefore, missing a sessile serrated polyp with cytologic dysplasia may (relative to missing other precancerous lesions) place patients at high risk of postcolonoscopy cancer.

G&H How does microsatellite instability in the serrated pathway relate to microsatellite instability in Lynch syndrome?

DR The CpG island methylator phenotype (CIMP) is characteristic of tumors arising through the serrated pathway. The CIMP acronym is based on the high level of hypermethylation in CIMP-positive tumors. Approximately half of CIMP-positive tumors are microsatellite unstable, and as previously noted, this is related to epigenetic inactivation of *MLH1*. Because 20% to 30% of all colorectal cancers are CIMP positive, approximately 10% to 12% of all colorectal cancers are microsatellite unstable and CIMP positive.

Lynch syndrome is an inherited cancer syndrome in which more than 90% of all tumors are microsatellite unstable. Lynch syndrome is caused by germline mutations in mismatch repair genes. Only approximately 3% of all colorectal cancers arise through the Lynch pathway. Thus, the serrated pathway accounts for approximately 80% of all microsatellite-unstable tumors. In clinical practice, it has become common to screen all colorectal cancers for microsatellite instability or failure to express the proteins encoded by mismatch repair genes in order to identify Lynch syndrome patients. Microsatellite instability or failure of mismatch repair protein expression caused by Lynch syndrome has to be differentiated from the more common scenario in which these same features occur in tumors in the serrated pathway.

G&H Could you discuss your recent study on the detection of proximal colonic serrated polyps across 32 centers?

DR This was an evaluation of a data set generated by Epigenomics to study their blood test for colorectal cancer (the Septin9 assay), in which colonoscopy had been performed in more than 7000 subjects. The primary results of this multinational multicenter study were published in *Gut* by Church and colleagues. My colleagues and I performed a secondary analysis looking at variation among the sites in the detection and pathologic assessment of polyps in the serrated class. Our analysis did have some limitations, in that not every polyp removed from patients with more than 3 polyps was represented in the database, and there was no central interpretation of the pathology findings. We used the pathology interpretation provided by local pathologists in the individual centers.

Two previous studies, one from Boston University and the other from my own center, had shown that individual gastroenterologists vary a good deal in the detection of serrated lesions. The purpose of the current analysis was to see whether similar variation was evident when centers were compared, rather than individual colonoscopists. Our analysis showed that there was indeed large variation in the detection of serrated polyps, and there was also a lot of variation in the interpretation of these polyps by pathologists.

G&H How did you interpret the finding that the term serrated polyp never appeared in pathology reports in 10 of the centers?

DR That finding reflects that some pathologists are just really learning about the serrated class of lesions. Pathologists in some of the centers may not be well informed about serrated lesions, may not have knowledge of the recommended terminology, may not be trained in the differentiation of serrated subtypes, or may feel that the differentiation of sessile serrated polyps from hyperplastic polyps lacks proven clinical importance. Regardless of the reasons, our study demonstrated a large variation among pathologists across the centers in the interpretation of these lesions.

G&H What are your recommendations for improving the yield of serrated polyps at screening colonoscopy?

DR There are several things that endoscopists can do to improve the detection of serrated polyps. The first is to prescribe effective bowel preparations for colonoscopy. Serrated polyps are more common in the proximal colon, and we know that some types of bowel preparations, particularly traditional evening-before bowel preparations, are not as effective at preparing the right colon as are split-dose bowel preparations. Therefore, the first thing that endoscopists should do is to utilize split-dose bowel preparations consistently. The second way to improve the detection of these polyps is to read about them and to review endoscopic picture sets that are available on the Internet. Lesion recognition starts with familiarity and understanding. A third way that endoscopists can improve the yield of serrated polyps is to transition to high-definition colonoscopes. We do not have specific data showing that high-definition colonoscopy is essential for the detection of serrated polyps, but we have seen fairly convincing evidence that it increases the detection of conventional adenomas. I predict that when high-definition colonoscopy is studied for the detection of serrated polyps, it will be shown to improve detection because these polyps are

more subtle than conventional adenomas, and improved image resolution should add more to their detection.

The final way that endoscopists can improve detection is to confer with pathologists in their institution to make sure that the pathologists are familiar with the World Health Organization (WHO) recommended histologic criteria for the diagnosis of sessile serrated polyps and with the terminology used in describing the serrated class of lesions. The pathologists and the endoscopists in an institution must both be fully up to speed and on the same page for the optimal diagnosis and management of sessile serrated polyps. There are several good resources to share to accomplish this goal, including WHO publications on this issue and a review article in the October 2012 issue of the *American Journal of Gastroenterology* from a National Institutes of Health expert consensus panel, which covers all aspects of the clinical features and pathology of serrated polyps. A number of pathologists are coauthors of this article, including experts from the WHO committee, so it is a good resource for endoscopists to take to pathologists in their institution so they can work together to improve the management of these polyps and use terminology that both groups understand. We need to maximize, on the part of endoscopists, the recognition of serrated polyps and, on the part of pathologists, the accurate differentiation of these polyps from hyperplastic polyps.

Dr Rex has been a consultant to Epigenomics, Inc.

Suggested Reading

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