A Colonoscopist’s Perspective on Serrated Lesions

Effective detection and resection of serrated class lesions is emerging as a defining feature of superior quality colonoscopy. Serrated lesions are more likely to be missed by colonoscopists compared to conventional adenomas, and effective detection depends on a well-informed endoscopist, high quality bowel preparation and detailed mucosal inspection. Serrated lesions are also more likely to be incompletely resected compared to conventional adenomas, but this problem can be overcome by submucosal injection with a contrast agent and use of a high definition colonoscope. Endoscopists and pathologists are both reliable in classifying colorectal lesions as belonging to the serrated class vs conventional adenomas. Endoscopists can utilize the NICE classification to make this distinction. There is a high level of interobserver variation between pathologists in the interpretation of hyperplastic polyp vs sessile serrated polyp (synonymous with sessile serrated adenoma). The NICE classification does not attempt to distinguish hyperplastic polyp from sessile serrated polyp, but the recently proposed WASP classification addresses this distinction. Most sessile serrated polyps have no cytological dysplasia, but about 5% of sessile serrated polyps contain a region that is endoscopically and histologically identical to a conventional adenoma. This lesion, termed a sessile serrated polyp with cytological dysplasia, is a more advanced lesion and must be completely resected and generally followed closely. Current recommendations for surveillance colonoscopy after resection of serrated are based on limited data, and are reviewed in this paper.

INTRODUCTION

SECTION 1

colorectal cancers are believed to arise almost entirely in benign growths called polyps. The conventional polyp to cancer sequence in the colorectum has been termed the “adenoma-carcinoma” sequence. This paper will refer to the precursor lesions in the adenoma-carcinoma sequence as “conventional adenomas.” By definition, all conventional adenomas are dysplastic, which should be characterized by pathologists as low-grade or high-grade dysplasia. In clinical practice, when conventional adenomas are reported without the dysplasia grade specified, clinicians can assume that the adenoma had low grade dysplasia. Conventional adenomas can also be characterized as tubular, tubulovillous, or villous.

Although every colorectal cancer has a unique molecular profile, there are 3 broad categories of molecular pathway to colorectal cancer. Conventional adenomas are the precursors of 2 of the pathways, including the chromosomal instability (CIN) pathway and the Lynch pathway (Table 1). In recent decades, there is increasing recognition that a third general molecular pathway to colorectal cancer arises through a precursor polyp that is distinct from the conventional adenomas. This separate set of polyps.
is the “serrated class” lesions, and these lesions are distinct from conventional adenomas in their molecular profile, their histology, and their endoscopic appearance. The serrated pathway accounts for 15 to 30% of all colorectal cancers, and the prevalence of cancers arising in serrated lesions increases progressively from the left to right side of the colon. Expertise in the recognition and effective resection of serrated class lesions has become one of the main distinguishing features of a modern master colonoscopist, compared to the average or low performing colonoscopist.

Terminology of Serrated Class Lesions

The World Health Organization (WHO) recommends division of the serrated class into three subtypes, including hyperplastic polyps, sessile serrated polyp (sessile serrated adenoma), and traditional serrated adenoma (Table 2).5 More than 99% of serrated class lesions fall into the hyperplastic polyp or sessile serrated polyp (SSP) subtypes. The terms “sessile serrated polyp” and “sessile serrated adenoma” (SSA) are synonymous. Clinical trials have commonly designated the lesions as either SSP or SSA or “SSP/SSA” to acknowledge that the two terms are interchangeable. The author is opposed to the term SSA, because the word “adenoma” has been traditionally understood by clinicians to be a dysplastic lesion (all conventional adenomas are dysplastic). However, more than 95% of all SSP/SSAs have no histologic dysplasia. Therefore, the term “SSP” engenders less confusion about the nature of these lesions. According to WHO, SSPs without dysplasia should be designated by pathologists as “SSP without cytological dysplasia.”

Less than 5% of SSPs have a region or portion that is histologically (and endoscopically) distinct from the SSP portion of the lesion in that it looks precisely like a conventional adenoma. In the past, such lesions were sometimes designated “mixed hyperplastic-adenomatous polyps.” The word “mixed” was a useful and accurate descriptor because these lesions are literally a mixture of SSP and conventional adenoma. According to WHO, these lesions should be designated as “SSP with cytological dysplasia,” and they are believed to represent a more advanced stage in the polyp-cancer sequence. About half of all serrated pathway cancers demonstrate microsatellite instability, generally attributable to epigenetic (hypermethylation driven) inactivation of the MLH1 gene.3,4 The SSP with cytological dysplasia has a high prevalence of microsatellite instability, which microdissection studies show is frequently localized to the dysplastic portion of the lesion.6

The traditional serrated adenoma (TSA) is a rare lesion, located primarily in the left colon, and is the only consistently dysplastic member of the serrated class. The molecular profile of TSA is variable and TSA is relatively poorly understood compared to SSP and HP.7

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Precursor Lesion</th>
<th>Speed of Polyp-Cancer Sequence</th>
<th>Common Mutations</th>
<th>Microsatellite Instability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal Instability</td>
<td>Conventional adenoma</td>
<td>Slow</td>
<td>APC, P53, Kras</td>
<td>No</td>
</tr>
<tr>
<td>Lynch</td>
<td>Conventional adenoma</td>
<td>Fast</td>
<td>MMR genes: MLH1, MSH2, MLH6, PMS2</td>
<td>Yes</td>
</tr>
<tr>
<td>Serrated (Hypermethylation)</td>
<td>Serrated lesions</td>
<td>Uncertain</td>
<td>BRAF</td>
<td>About 50%</td>
</tr>
</tbody>
</table>

Table 2. World Health Organization Classification of Serrated Lesions

Hyperplastic Polyp

Sessile Serrated Polyp
- Without cytological dysplasia
- With cytological dysplasia

Traditional Serrated Adenoma
Problems with Pathologic Interpretation of Serrated Class Lesions

The pathologic distinction between HP and SSP is subject to marked interobserver variation between pathologists.8-10 The principal histologic distinction between HP and SSP is in crypt morphology, with crypts being straight and non-dilated in HP while SSP demonstrates dilation, distortion, and/or lateral crypt growth. The first problem in pathologic differentiation of HP from SSP arises because different expert bodies have different definitions (none of which have been validated) of the number of abnormal crypts or the percentage of abnormal crypts that must be present to identify SSP. The second problem is that when the number of affected crypts is small, there is marked interobserver variation between pathologists (even experts) in interpreting HP versus SSP.8-10 A third problem is that some pathologists are either unaware of or refuse to acknowledge SSP. Thus in a multicenter trial from the U.S. and Germany involving > 7000 screening colonoscopies, some centers never reported SSP, though there were multiple HPs > 1 cm in size.11 Within centers, the percentage of serrated class lesions called SSP has often increased steadily over the past decade, suggesting that awareness of SSP among pathologists is increasing.12 These problems with differentiation of SSP from HP have created uncertainty among clinicians.

(continued on page 30)
regarding the reliability of pathologic assessment of serrated class lesions, so that some clinicians treat HPs > 1 cm removed from the proximal colon as SSP and guidelines support this practice.\(^2\)

The traditional serrated adenoma (TSA) represents another challenge for the clinical pathologist. As TSA is the only consistently dysplastic lesion in the serrated class and commonly has a villiform growth pattern, in clinical practice it is commonly misidentified as a tubulovillous conventional adenoma. Thus, many clinicians have never seen the term “traditional serrated adenoma” on a pathology report.

Endoscopic Detection of SSP
Colonoscopic detection of SSP is subject to even more marked variability between colonoscopists than detection of conventional adenomas.\(^2,13\) SSPs are invariably sessile or flat, and many large SSPs are almost completely flat. SSPs are pale in color, and similar in colon to the surrounding mucosa, though the lesions typically obscure the colonic vascular pattern.\(^14,15\) The surface texture of serrated class lesions is usually slightly rougher and more granular than the normal mucosa, which contributes to detection. A “cap” of adherent mucus is often an important clue to detection of serrated class lesions. HP and SSP
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share many endoscopic features, and are more easily distinguished from conventional adenomas than from each other. The Narrow band imaging International Colorectal Endoscopic (NICE) classification for narrow-band imaging (NBI) optical diagnosis of colorectal polyps presents criteria for differentiation of conventional adenomas from serrated class lesions, but makes no attempt to differentiate HP from SSP.16 In NICE, serrated class lesions are distinguished by having no blood vessels on their surface, or only a few lacy blood vessels that course past multiple pits, uniform or relatively uniform sized pits, and pale color (Figure 1). The NICE classification has been utilized in multiple studies to accurately distinguish serrated class lesions from conventional adenomas.17-19 Recently, the Workgroup serrAteled polypS and Polyposis (WASP) classification has been developed to distinguish SSP from HP. Features that distinguish SSP, particularly when all are present, include large open pits, an irregular surface, indiscrete edges, and “cloud-like features” (Figure 2).20 Endoscopically, the sessile serrated polyp with cytological dysplasia presents as regions that are partly NICE Type I and partly NICE Type 2 (Figure 3). Accurate detection of serrated class lesions depends

Figure 3a. Sessile serrated polyp (SSP) with cytological dysplasia. The typical SSP portion is at the base (yellow arrows) and the dysplastic portion at the tip (red arrows) (NBI).

Figure 3b. Sessile serrated polyp with cytological dysplasia after submucosal injection with hydroxyethyl starch and indigo carmine. Yellow arrows mark the edge of the SSP portion. A black irregular line surrounds the dysplastic portion (white light).

Figure 4a. A 33mm sessile serrated polyp in ascending colon with mucus cap and adherent debris (white light).

Figure 4b. The same lesion after submucosal injection of the right side with hydroxyethyl starch and indigo carmine. Note the excellent delineation of the right margin (white light).
on excellent bowel preparation, a colonoscopist with a complete understanding of the spectrum of endoscopic appearances of SSP, and a high definition colonoscope. Meticulous technique in looking behind folds, achieving adequate distention, and cleaning up pools of residual liquid and fecal debris are essential. When the first examination of the right colon reveals lesions, a second repeat examination in either the forward or retroflexed view should be considered.

Optimal Techniques for Resection for SSP

The CARE study evaluated predictors of incomplete colorectal polyp resection for lesions 5 to 20 mm in size. Predictors of incomplete resection included larger polyp size, the endoscopist, and serrated histology. The overall risk of incomplete resection of serrated class lesions was 31%, compared to 7% for conventional adenomas, and half of serrated class lesions 10-20 mm in size were incompletely resected. The methods of endoscopic resection in the CARE study were not described.

The challenge in resecting serrated class lesions almost certainly arises because of their indistinct edges. With resection of large lesions, particularly in piecemeal fashion, the operator can lose track of the perimeter of the lesion and thereby fail to achieve complete resection.

In contrast to CARE, 2 recent studies have found that endoscopic mucosal resection (EMR) eradicates SSP as effectively as it treats conventional adenomas. One included lesions only ≥ 20 mm in size, and one included predominantly 10-20 mm lesions. The keys to effective resection appear to be submucosal injection with a contrast agent (indigo carmine or methylene blue) and use of a high definition scope. These tools allow the endoscopist to effectively demarcate the lesion perimeter and keep track of residual abnormal crypts as the resection proceeds (Figure 4). These studies indicate that colonoscopists should have a low threshold (10 mm) for performing EMR for serrated class lesions.
Follow-up of Serrated Lesions

There are very few observational studies describing the risk of cancer or advanced neoplasms after resection of serrated class lesions. Early recommendations will certainly be adjusted as new data become available. The U.S. Multi Society Task Force recommendations (Table 3) rely heavily on the pathologist’s report of HP versus SSP, though they endorse the practice of treating HPs ≥ 10 mm from the proximal colon as SSP. This is particularly appropriate when clinicians rarely see SSP reported by their pathologists.

The National Institutes of Health expert consensus panel recommendations suggest that clinicians consider the size, histology, number, and location of serrated class lesions to choose a surveillance interval (Table 4). Proximal location, increasing number of lesions, increasing lesion size, pathologist interpretation of SSP over HP, and SSP with cytological dysplasia are all considered to have predictive value. Either set of recommendations represent a reasonable framework for choosing post polypectomy surveillance intervals after resection of serrated class lesions.

Choosing appropriate surveillance intervals is no substitute for adequate detection during baseline examinations. Overall, detection of serrated class lesions is reasonably correlated with detection of conventional adenomas, and the primary measure of mucosal inspection quality should be the adenoma detection rate (ADR). Currently, although detection of serrated lesions is considered very important, the use of a specific target for detection of serrated lesions is not feasible because it would need to be confined to the proximal colon (and therefore subject to endoscopist inaccuracy in assessing location) and the marked pathologist interobserver variation in differentiating SSP from HP.

Table 4. NIH Consensus Panel Recommendations for Surveillance Colonoscopy After Resection of Serrated Lesions

<table>
<thead>
<tr>
<th>Colonoscopy Finding</th>
<th>Number Lesions</th>
<th>Recommended Intervals</th>
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<tbody>
<tr>
<td>SSP with dysplasia</td>
<td>Any</td>
<td>1-3 years</td>
</tr>
<tr>
<td>SSP ≥ 10mm</td>
<td>≥ 2</td>
<td>1-3 years</td>
</tr>
<tr>
<td>SSP or TSA ≥ 10mm</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>SSP or TSA &lt; 10mm</td>
<td>≥ 3</td>
<td>3</td>
</tr>
<tr>
<td>SSP or TSA &lt; 10mm</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>HP &gt; 5mm</td>
<td>≥ 1</td>
<td>Proximal to sigmoid</td>
</tr>
<tr>
<td>HP any size</td>
<td>≥ 4</td>
<td>Proximal to sigmoid</td>
</tr>
<tr>
<td>HP ≤ 5mm</td>
<td>≤ 3</td>
<td>Proximal to sigmoid</td>
</tr>
<tr>
<td>HP &lt; 10mm</td>
<td>Any number in recto-sigmoid</td>
<td>10</td>
</tr>
</tbody>
</table>

SSP: Sessile serrated polyp  
TSA: Traditional serrated adenoma  
HP: Hyperplastic polyp

Table 5. World Health Organization Criteria for Serrated Polyposis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Criteria 1</td>
<td>5 or more serrated class lesions proximal to sigmoid with at least 2 &gt; 10 mm in size</td>
</tr>
<tr>
<td>Criteria 2</td>
<td>Any serrated class lesion proximal to the sigmoid in a first degree relative of a patient with serrated polyposis</td>
</tr>
<tr>
<td>Criteria 3</td>
<td>20 or more serrated class lesions located throughout the colon</td>
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</tbody>
</table>
Serrated Polyps

Serrated polyposis (formerly hyperplastic polyposis syndrome) is by far the most common polyph syndrome in clinical practice.29,30 The WHO presents 3 criteria for the diagnosis of serrated polyposis (Table 5). The diagnosis is frequently missed in clinical practice, and high sensitivity requires counting the number and size of lesions by location, and comparing to the WHO criteria.

The risk of cancer in serrated polyposis is most related to the number of large proximal colon SSPs and the presence of SSPs with dysplasia.29,30 Patients with serrated polyposis have a significant risk of colorectal cancer that can be managed by effective colonoscopic surveillance, usually performed at 1-2 year intervals.29,30 First-degree relatives of patients with serrated polyposis should undergo an initial screening colonoscopy at age 40, and then every 5 years if the baseline examination is negative.

SUMMARY AND CONCLUSIONS

The serrated or hypermethylated pathway to colorectal cancer proceeds through a distinct class of precursor lesions with unique molecular, histologic and endoscopic appearances. A full understanding of the spectrum of endoscopic appearances, as well as methods of effective resection, are essential to modern colonoscopic management of serrated lesions and to effective colonoscopy in general. EMR using a contrast agent and a high definition colonoscope effectively eradicates serrated class lesions. Endoscopists should have a high level of suspicion for serrated polyposis in patients with multiple serrated lesions, and compare polyp counts to WHO criteria for diagnosis of this syndrome.

References