REVIEW ARTICLE

The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management

Douglas K. Rex, MD,[1] Cesare Hassan, MD,[2] Michael J. Bourke, MD[3]

Indianapolis, Indiana, USA; Rome, Italy; Sydney, Australia

Prevention of colorectal cancer by colonoscopy requires an effective and safe insertion technique, a high level of detection of pre-cancerous lesions, and skillful use of curative endoscopic resection techniques. Lesion detection, characterization, use of appropriate resection methods, prediction of cancer at colonoscopy, and management of malignant polyps all depend on an accurate and complete understanding of an extensive vocabulary describing the histology and morphology of neoplastic colorectal lesions. Incomplete understanding of vocabulary terms can lead to management errors. We provide a colonoscopist's perspective on the vocabulary of colorectal neoplasia and discuss the interaction of specific terms with management decisions.

Nearly 60% of the eligible U.S. population report being up to date with colorectal cancer screening, with colonoscopy the most commonly used screening test.[1] Many gastroenterologists spend more time performing colonoscopy than any other professional activity. One would expect gastroenterologists to be expert in all aspects of the vocabulary of colorectal neoplasia, including histologic and morphologic classifications of polypoid and flat lesions.

However, speaking to groups of gastroenterologists and other endoscopists, the responses to fundamental questions about colorectal neoplasia are often surprising. For example: How reliable is a pathologist's designation of dysplasia grade in a conventional adenoma? Why is the term "dysplastic adenoma" redundant? Why should the term "intramucosal adenocarcinoma" not be used in pathology reports? What is the histologic difference between a hyperplastic polyp (HP) and a sessile serrated polyp/adenoma? What are the implications of granular versus non-granular morphology in a lateral-spreading tumor? What is the histologic definition of colon cancer?

The answers to these and similar questions provide colonoscopists with critical insights into the limitations of pathology, the proper responses to pathologic interpretations of colon polyps, and in many cases to optimal endoscopic, clinical, or surgical management. A detailed understanding of the implications of both endoscopic appearances and histology is critical in guiding the colonoscopist. The modern expert colonoscopist is able to use electronic chromoendoscopy techniques and established classification schemes to predict lesion histology. Thus, an expert colonoscopist is able to differentiate between a serrated and adenomatous polyp, and between a deeply invasive cancer versus superficial colorectal neoplasia. This review provides a clinically oriented framework to the vocabulary surrounding the main classes of colorectal lesions, particularly the conventional adenomas and serrated lesions. The implications of this vocabulary on management and follow-up are stressed, including how the endoscopic assessment of histology and morphology direct the selection of specific therapies such as EMR, endoscopic submucosal dissection (ESD), and surgical resection.

What are EMR and ESD?

EMR refers to submucosal fluid injection followed by en bloc or piecemeal snare resection. EMR is easier to perform than ESD, requires less training, has a much lower risk of perforation, and a lower need for hospitalization after resection. EMR may be technically quite difficult when lesions are very large, very flat, in a technically challenging position, or when they are accompanied by submucosal fibrosis. Both EMR and ESD have substantial risks of delayed post-polypectomy hemorrhage. For these reasons, many patients with colorectal lesions that are benign and removable by EMR are sent directly to surgery in the United States and Europe,[2,3] even though surgery results in higher costs, morbidity, and mortality than EMR.[4-6]

Abbreviations: ESD, endoscopic submucosal dissection; HP, hyperplastic polyp; JNET, Japan NBI Expert Team; LST, lateral-spreading tumor; MM, muscularis mucosa; NICE, Narrow-band Imaging International Colorectal Endoscopic classification; SSP, sessile serrated polyp; TSA, traditional serrated adenomas; SSA/P, sessile serrated adenoma/polyp.

DISCLOSURE: *Dr Rex has received research support from Boston Scientific, Endochoice, and EndoAid, and has acted as consultant and received honoraria from Boston Scientific. Dr Hassan has acted as consultant for Olympus, Fujinon, and Endochoice.*

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2017.03.1546

(footnotes continued on last page of article)

ESD was developed in Japan to treat early gastric cancer. ESD has been extended to the colon, where it has been used successfully by Japanese experts[7-9] and increasingly by western experts.[10-12] The technique involves submucosal injection, but ESD does not use snare resection. Specialized endoscopic needle-like knives are used to create a circumferential incision through the mucosa around the lesion, followed by dissection through the submucosa under the lesion. The goal of ESD is en bloc resection in all cases, and ESD is much more likely than EMR to achieve this result.[13] The en bloc tissue specimen is pinned before fixation to provide proper orientation for pathologic assessment of the deep and lateral resection margins. Whether ESD should be used more extensively in the West is controversial. Given the advantages of EMR relative to ESD noted above, which patients and how many patients really benefit from ESD compared with EMR is a critical issue that is discussed in detail below.

The colonoscopist's vocabulary of colorectal cancer

Because the colon has no mucosal lymphatics, colon cancer is defined in western countries as invasion of dysplastic cells into the submucosa. It follows that any neoplastic lesion that is confined to the mucosa, including epithelium, lamina propria, and muscularis mucosa, must be considered pre-cancerous or non-invasive, irrespective of its dysplastic or cytologic appearance, and is best named as low- or high-grade dysplasia. Some pathologists still use terms such as "carcinoma in situ" and "intramucosal adenocarcinoma" to describe lesions involving severe dysplastic changes confined to the epithelium or lamina propria, respectively. However, these terms are often misinterpreted by patients, referring physicians, and sometimes by colonoscopists, as cancer because they include the word "carcinoma." This confusion can result in unnecessary surgery or excessive follow-up for a lesion that is benign by definition. Such lesions have no lymph node or distant metastatic potential because they lack submucosal invasion, and complete endoscopic resection is uniformly curative.[14] Current U.S. National Comprehensive Cancer Network guidelines specifically state, "A malignant polyp is defined as one with cancer invading through the muscularis mucosa and into the submucosa (T1). Tis is not considered a 'malignant polyp'" (https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf). We recommend that colonoscopists meet with their pathologists to reach consensus regarding optimal terminology, and that colonoscopists take the position that pathologists report "high-grade dysplasia" and not use the terms "intramucosal carcinoma" or "carcinoma in situ," in order to reduce the potential for clinical management errors (Table 1). Western colonoscopists may also be confused because Japanese pathologists and gastroenterologists commonly use the term "intramucosal carcinoma" and count it as cancer. This difference is related to cultural and economic issues, whereas no clinical difference is present, ie, endoscopy is still considered completely adequate treatment for such lesions in Japan. We recommend that, in western countries, the terms "carcinoma in situ" and "intramucosal carcinoma" be abandoned because they may lead to incorrect patient management. Terminology should serve patients and physicians by optimizing rather than confusing management, and hence the term cancer is reserved (in the colorectum) in western countries exclusively for submucosal invasion.

TABLE 1. Pathology terms we could do without

Confusing term	Better term
Carcinoma in situ, intramucosal adenocarcinoma	High-grade dysplasia
Sessile serrated adenoma, serrated adenoma	Sessile serrated polyp

What is superficial versus deep submucosal cancer?

When submucosal cancer is present in a pedunculated polyp, endoscopy is usually regarded as an adequate treatment when 3 histologic factors, namely cancer at the resection margin, lympho-vascular invasion, and poor differentiation, are absent.[13] When invasive cancer is present in a flat (ie, non-polypoid) or sessile lesion, the depth of invasion below the muscularis mucosa (MM) should be measured by the pathologist when technically feasible. If the depth is <1000 μm, the submucosal cancer is classified as "superficial." If the depth of invasion is >1000 μm, the cancer demonstrates "deep submucosal invasion." There are elements of subjectivity with this measurement because the MM layer may be disrupted or not visible. Reliable measurement of the depth of invasion is generally considered to require en bloc resection of the lesion by conventional snare techniques for smaller lesions and either en bloc EMR or ESD for lesions >10 to 20 mm. Pinning the lesion to allow proper orientation for histologic sectioning is important.[12,13] When a superficial submucosal cancer does not present lympho-vascular invasion or poor differentiation after an en bloc resection, endoscopic treatment may be considered as adequate because of a very low risk of lymph node metastasis. In contrast, the risk of lymph node metastasis increases substantially when deep submucosal invasion is present.

When deep submucosal invasion is predicted by endoscopic features,[15] it is preferable to avoid endoscopic resection and proceed to surgery. This prevents the risk of endoscopic adverse events, and endoscopic resection followed by pathology demonstrating deep submucosal invasion will result in surgery in any case. If superficial

TABLE 2. Narrow-band imaging (NBI) International Colorectal Endoscopic (NICE) Classification*

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures†	Has area(s) of disrupted or missing vessels
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structures† surrounded by brown vessels	Amorphous or absent surface pattern
Most likely pathology	Hyperplastic & sessile serrated polyp (SSP)‡	Adenoma§	Deep submucosal invasive cancer

*Can be applied using colonoscopes with/without optical (zoom) magnification.
†These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.
‡In the WHO classification, sessile serrated polyp and sessile serrated adenoma are synonymous. SSPs often demonstrate some dark, dilated crypt orifices.
§Type 2 consists of Vienna classification types 3, 4, and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (eg, depressed area).

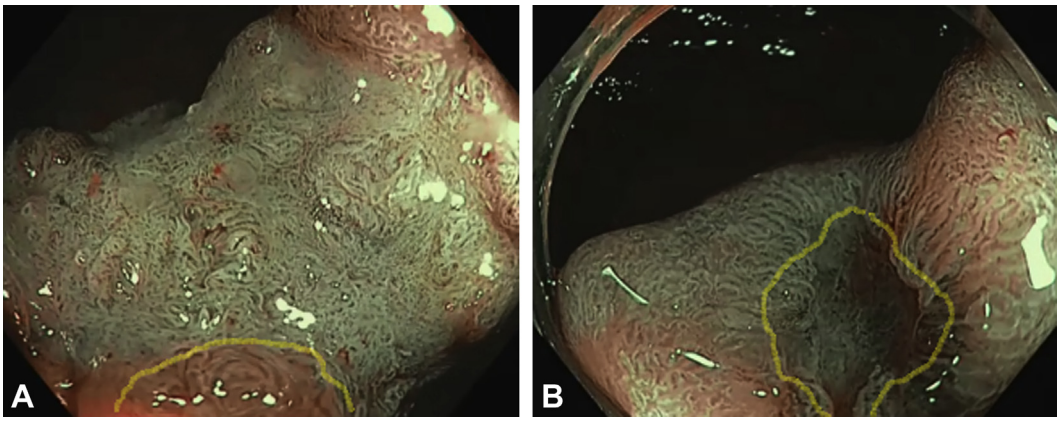

Figure 1. Lesions with NICE type 3 features indicating deep submucosal invasion. In **A,** much of the lesion shows type 3 features with a disrupted amorphous blood vessel pattern. The yellow line overlies one of the areas of NICE type 2 features, indicating residual intact adenoma. In **B,** most of the lesion has NICE type 2 features but the area surrounded by the yellow line has a disrupted vascular pattern consistent with NICE type 3 and indicative of deep submucosal invasion.

invasion is identified after piecemeal snare resection of a flat or sessile lesion, surgical resection is often still considered because of the risk of understaging a potentially deeply invasive cancer, especially if adequate orientation of the specimen by the pathologist is not feasible. This difference highlights the benefit of en bloc resection. With en bloc resection of a sessile or flat lesion and proper specimen orientation, the patient with superficial invasion (and lacking other adverse histologic features) has the option of relying on endoscopic resection alone, because the risk of lymph node metastasis is very low (although not 0). In the West, many patients in this situation, especially if they are young (eg, <60 years old) and healthy, will select surgical resection even when all histologic criteria associated with submucosal invasion are favorable, because the risk of metastasis with favorable criteria is very low but not 0. Again, when the same lesion has been treated by piecemeal snare resection, confidence in whether adequate treatment has been provided by endoscopy is undermined.

Endoscopic predictors of deep (>1000 μm) submucosal invasion in flat and sessile lesions are described in the type 3 category of the Narrow-band Imaging International Colorectal Endoscopic (NICE) classification[15,16] (Table 2). Identification of NICE type 3 features in a flat or sessile lesion is generally an indication for surgical resection (Fig. 1). If surgery is planned, a biopsy sample from the NICE type 3 area can be examined to confirm invasive cancer. In Japan, reliance on NICE alone to predict cancer endoscopically is considered inadequate, because the magnifying endoscopes widely used in Japan can identify features that extend the predictions achievable with the high-definition instruments commonly in use in North America and Europe. These features are summarized in the Japan NBI Expert Team (JNET) classification for magnifying colonoscopy.[17] Widespread use of the JNET classification in the West, where magnifying

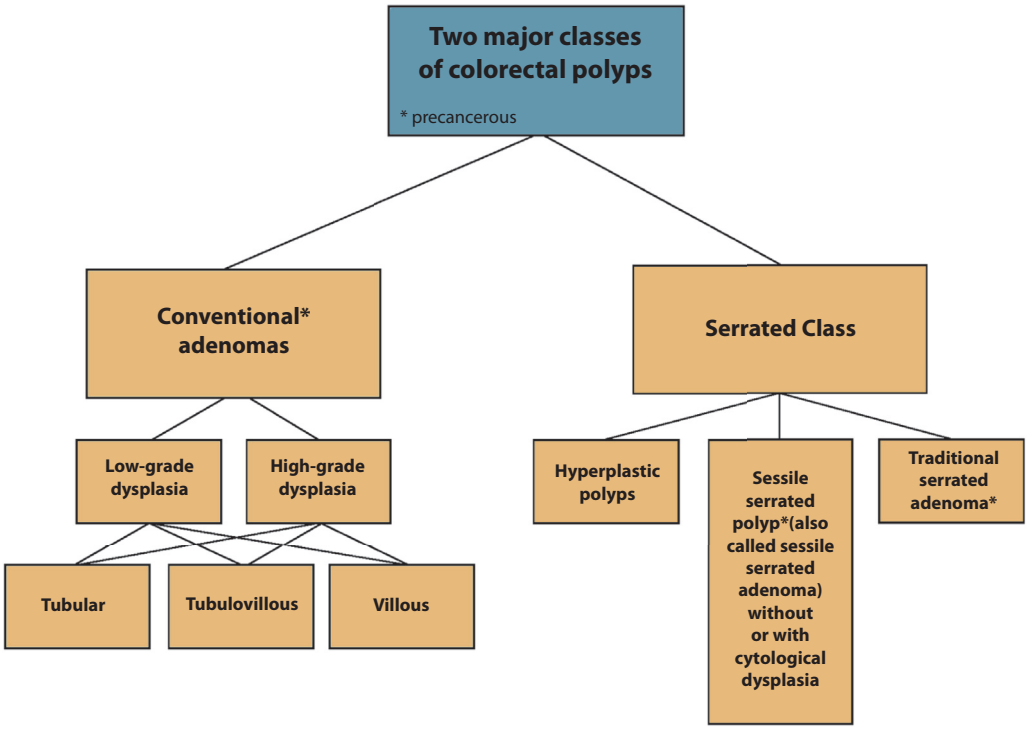

Figure 2. The 2 major classes of colorectal polyps. Asterisks denote the pre-cancerous lesions, which include all of the conventional adenomas and all of the serrated class lesions except the hyperplastic polyps.

TABLE 3. Areas of good and poor agreement between pathologists in colon polyp interpretation

Good agreement	1. Assigning polyps to the conventional adenoma vs serrated class (Fig. 2) 2. Identifying submucosal invasion (colon cancer)
Poor agreement	1. Designating dysplasia grade in conventional adenomas 2. Determining tubular vs tubulovillous in conventional adenomas 3. Designating serrated class lesions as sessile serrated polyp vs hyperplastic polyp

colonoscopes are not widely used, is not anticipated in the near future.

Unfortunately, no reliable endoscopic features differentiate superficial submucosal invasion from high-grade dysplasia.[15,16] However, some endoscopic morphologic features are associated with a higher risk of submucosal invasion, namely non-granular lateral-spreading tumors (LSTs), particularly those with a focal depressed component, and to a lesser extent large mixed-type granular lesions (granular lesions with nodules).[18] The term "LST" refers to a flat or sessile lesion with a diameter of at least 1 cm.[19] The morphology of LSTs and the association with invasive cancer are discussed in more detail below.

As noted above, patients who will benefit from ESD rather than piecemeal EMR are those with superficial submucosal invasion that cannot be removed en bloc by EMR. In European series, this group is about 2% to 3% of patients referred for resection of large colorectal lesions.[10-12] In Japanese series, 7% to 10% of colorectal lesions subjected to ESD have superficial invasion, reflecting better patient selection for ESD (higher fraction of non-granular LSTs).[7-9] Non-granular LSTs >20 mm in size (en bloc excision by EMR is generally limited to lesions ≤20 mm) with focal depression and lacking NICE type 3 features are the best candidates for ESD in the colorectum, as they have the highest rate of superficial submucosal invasion. EMR can still be used to treat these lesions, but the patient may be referred for surgery if there is submucosal invasion, regardless of the depth of invasion.

The vocabulary of conventional adenomas

The main histologic classes of pre-cancerous colorectal neoplasia are the conventional adenomas and the serrated class lesions (Fig. 2). Pathologists are generally accurate in assigning lesions to the conventional adenomas versus the serrated class.[20] Experienced colonoscopists are also

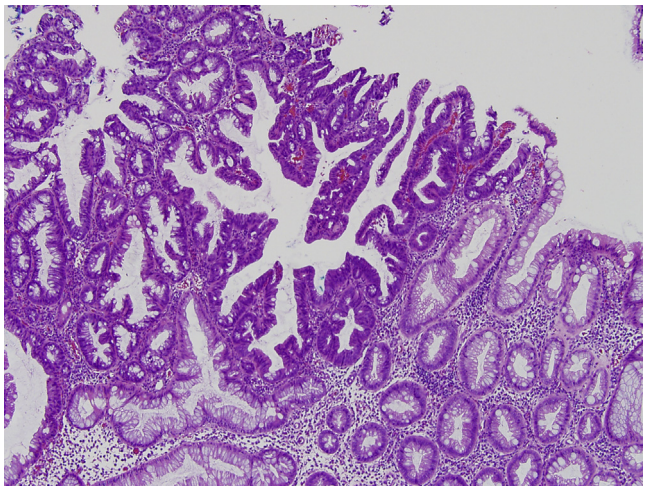

Figure 3. A sessile serrated polyp with cytologic dysplasia. The dysplastic portion of the polyp is to the upper left. To the right is a typical non-dysplastic sessile serrated polyp.

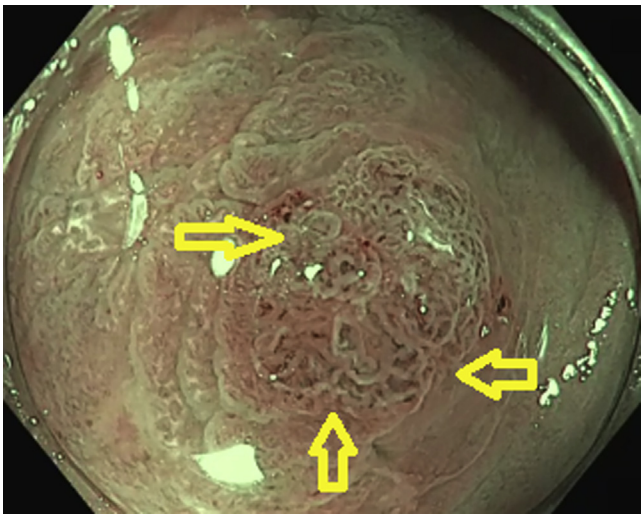

Figure 4. A sessile serrated polyp with cytologic dysplasia (same lesion as in Fig. 3). The arrows point to a brown nodule on the polyp surface. The nodule is the dysplastic portion of the polyp.

effective at predicting the histologic class of specific lesions using criteria such as NICE (Table 2).

Pathologists subclassify conventional adenomas according to the dysplasia grade (low versus high is the proper designation; mild, moderate, severe are outdated), and tubular versus villous elements. Although the placement of lesions into the conventional adenoma category by the pathologist is reliable, the subclassifications are unreliable.[20] Stated differently, they are subject to substantial interobserver variation (Table 3), and this is particularly true in their application to polyps <1 cm in size.[21] This size group is of particular relevance because polyps ≥1 cm in size are considered advanced lesions based on their size alone, whereas lesions <1 cm in size are not advanced unless they have either high-grade dysplasia or villous elements. The overwhelming majority of adenomas are tubular, that is, they contain ≥75% tubular elements. Using identical definitions, pathologists vary by up to 6-fold in the frequency with which they call polyps tubulovillous.[21] Problems with interpretations of dysplasia grade are even greater because there is no clear consensus on the definition of high-grade histology.[21] Pathologists who read high percentages of lesions with high-grade dysplasia are typically using cytologic criteria in addition to morphologic criteria. Any reading of high-grade dysplasia in a conventional adenoma <1 cm in size is suspect and may not withstand review by another or an expert gastrointestinal pathologist.[21] Currently, there are no reliable endoscopic criteria to differentiate dysplasia grade or villosity in a conventional adenoma, so colonoscopists must rely on the interpretation by pathologists. However, the expected prevalence of villous elements and high-grade dysplasia in 6 to 9 mm lesions is quite low, and even lower in conventional adenomas ≤5 mm in size.[22] The unreliability of pathologic interpretation of dysplasia grade and villosity is such that the British Society of Gastroenterology ignores these elements in their postpolypectomy surveillance guideline.[23]

TABLE 4. The Workgroup on serrAted polypS and Polyposis (WASP) criteria for endoscopic differentiation of sessile serrated polyp from hyperplastic polyp

Features that distinguish SSP from HP
Irregular surface
Indistinct edges
Cloud-like surface
Large open pits

Although diagnoses of dysplasia grade and villosity are subject to marked interobserver variation between pathologists, these factors are included as determinants of surveillance intervals in clinical guidelines. As noted above, the appropriateness of using these factors as surveillance determinants is controversial.

Using the NICE classification, expert colonoscopists can predict adenomatous versus serrated class histology with an accuracy similar to pathologists. This approach forms the basis of new paradigms for diminutive polyp management, including the "resect and discard" scheme and leaving distal colon diminutive hyperplastic-appearing polyps in place without resection.[24] Predicting adenomatous histology endoscopically is also important to the therapeutic colonoscopist. Specifically, the adenomas are a more challenging group of lesions to resect than the serrated lesions (see below). The adenomas can become very large (nearly circumferential and extending longitudinally over multiple haustral folds). Non-granular LSTs and the depressed class of

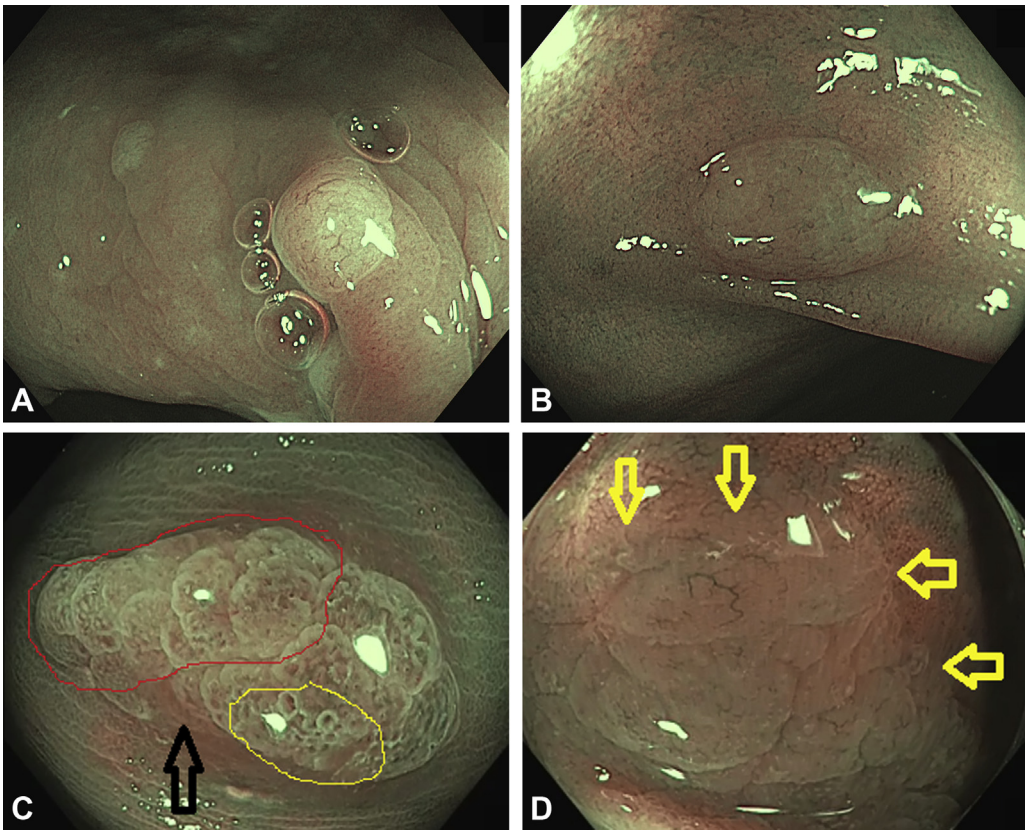

Figure 5. A and B, Typical hyperplastic polyps, which are pale from a paucity of blood vessels. The pits are uniform size and either pale (**A**) or dark (**B**). The few vessels are thin and lacy. **C and D**, Sessile serrated polyps. The *yellow line* in (**C**) outlines an area of large open pits. The red line outlines an area with cloud-like appearance. The *arrow* points to an indiscrete margin and the entire surface has the irregular surface contour of a sessile serrated polyp. In (**D**), the *arrows* outline the indiscrete edges of the lesion. **D** also demonstrates a cloud-like surface.

lesions are almost entirely adenomas. Adenomas are much more likely to have submucosal fibrosis than serrated lesions, and submucosal fibrosis is the bane of EMR. Serrated lesions present their own set of obstacles to endoscopic resection,[25] but they are usually easily overcome.

The vocabulary of serrated lesions

The "serrated class" includes 3 distinct groups of lesions: HPs, sessile serrated polyp (SSPs) (also called sessile serrated adenoma [SSAs]), and traditional serrated adenomas (TSAs) (Fig. 2).[26] TSAs are rare by comparison with the other 2 serrated class subtypes. TSAs are located mostly in the left side of the colon, are usually sessile, and are the only group of serrated class lesions that is consistently dysplastic.[27] Because they grow in a villous pattern and are dysplastic, TSAs may be interpreted by pathologists as tubulovillous adenomas.[27] This error appears to be made so consistently by some pathologists that colonoscopists often anecdotally report never seeing TSA on a pathology report. Because TSAs are rare, we focus here on the HPs and SSPs/SSAs, both of which are quite common.

As stated earlier, both pathologists and colonoscopists accurately place polyps into the conventional adenoma versus serrated class (with the exception of TSAs). Unlike the conventional adenomas and TSAs, all of the HPs and the overwhelming majority of SSPs are non-dysplastic.[27] SSP is synonymous with SSA,[26] but we prefer "sessile serrated polyp" in conversation and on pathology reports. This preference is because clinicians interpret the word "adenoma" to signify dysplasia (as noted above, all conventional adenomas are dysplastic). Thus, clinicians often believe that a "sessile serrated adenoma" must be dysplastic. Since most of these lesions are not dysplastic, we feel "SSP" causes less confusion for clinicians. Despite this preference, we acknowledge that neither "SSP" nor "SSA" is ideal from the perspective that many of these lesions are flat and not polyps (both terms contain the word "sessile"), and "SSP" could compound this confusion by including the word "polyp." Regardless of which term (SSP or SSA) is used, clinicians must understand that (1) SSP and SSA are synonyms, (2) these lesions can be either sessile or flat, and (3) these lesions are usually not dysplastic. To further acknowledge that SSP and SSA are synonyms, we refer to the lesions here by the commonly accepted acronym "SSA/P."[27]

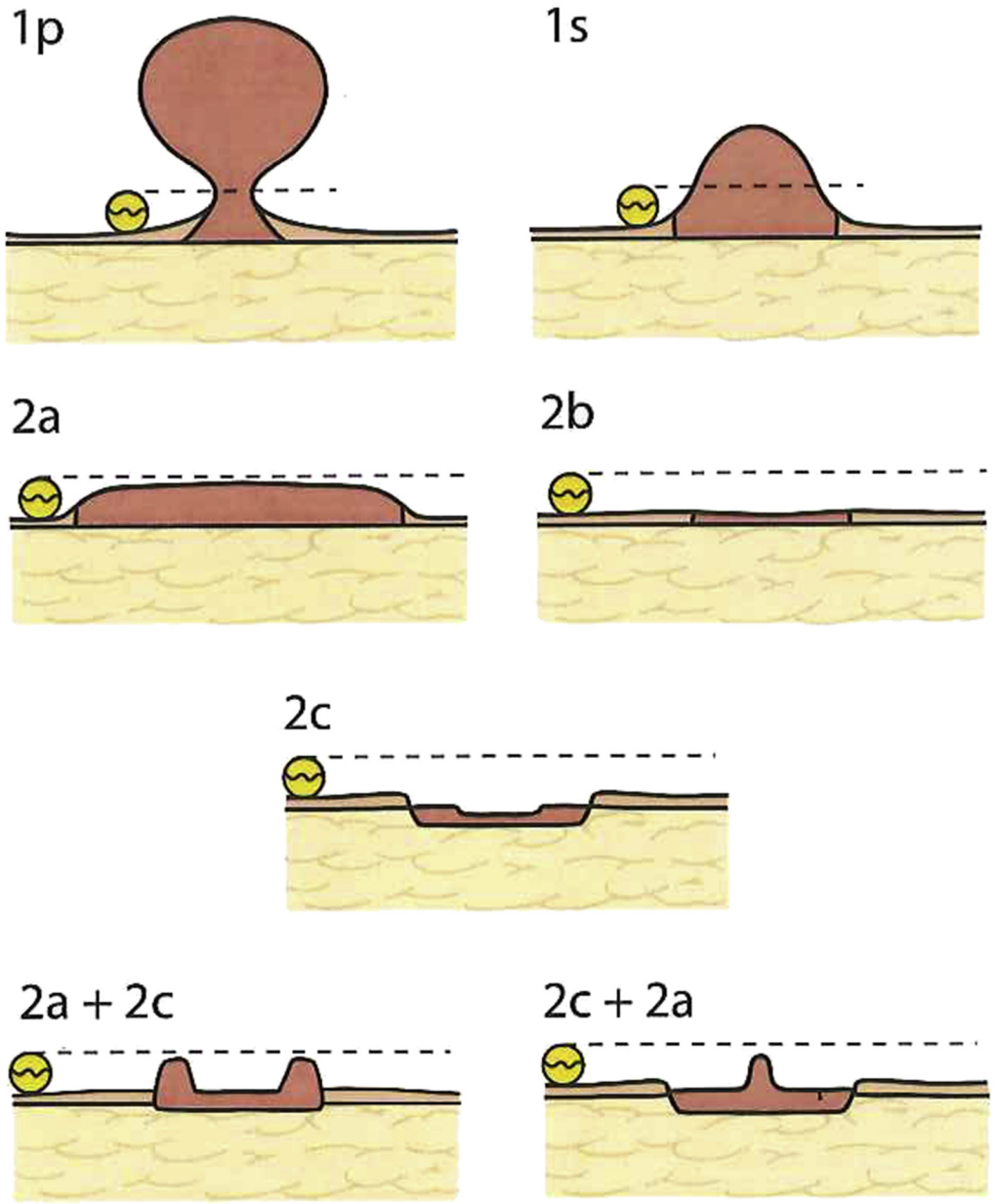

Figure 6. The Paris classification. Paris type 1 lesions are polyps. Type 2 lesions are flat and depressed lesions. Type 2a and 2b are flat and type 2c and its variants are depressed.

The histologic differentiation of an HP from an SSA/P rests primarily on the shape of crypts.[27] SSA/Ps have crypts that are dilated, distorted, or demonstrate lateral growth, whereas the crypts of hyperplastic polyps are straight. Unfortunately, no definition of the extent to which the crypts should be distorted has been validated as having clinical significance in distinguishing a group of polyps (SSA/Ps) with malignant potential and distinct behavior from HPs. Further, different histologic criteria for SSA/P are in use. For example, the World Health Organization recommends that 3 abnormal crypts constitute a diagnosis of SSA/P,[26] whereas a National Institutes of Health consensus panel recommended that one unequivocally abnormal crypt is diagnostic of SSA/P,[27] and the Japanese Pathology Society recommends that $\geq$10% of the crypt be affected to diagnose SSA/P.[28] When the number of crypts affected by distortion is small, there is substantial interobserver variation in differentiating HP from SSP.[29]

Although the overwhelming majority of SSA/Ps have no cytologic dysplasia (Table 3), a small percentage contain a region that looks like a conventional adenoma (Fig. 3). In decades past, this lesion was designated a "mixed hyperplastic-adenomatous polyp," which was perfectly

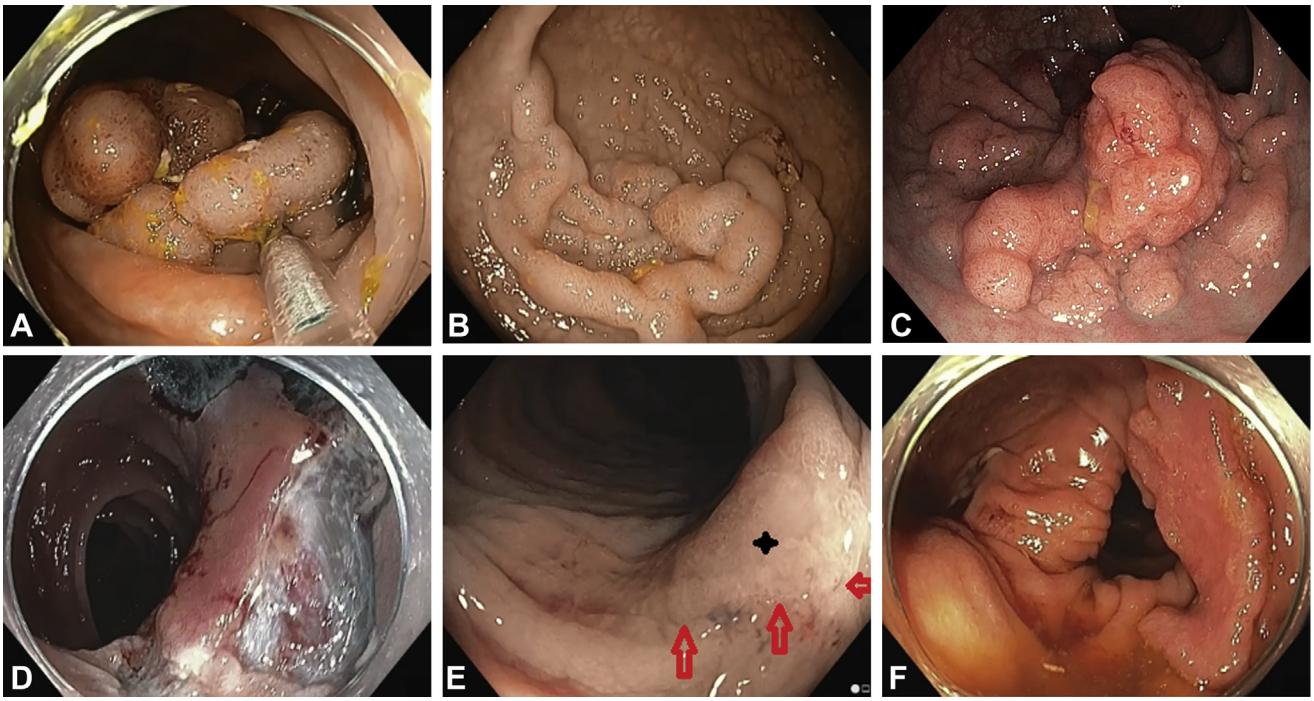

Figure 7. A and B, Granular lateral-spreading tumors (LSTs). The bumpy surface of the lesions leads to the "granular" name. Granular LSTs have a low risk of invasive cancer and are less likely to demonstrate significant submucosal fibrosis. **A**, a right-sided colon lesion about to undergo submucosal injection. **B**, A large rectal lesion. **C**, A granular LST with a large nodule. **D**, A large non-granular LST in the transverse colon during the process of resection. Note the smooth hard appearance of the residual lesion, which leads to the "non-granular" terminology. Non-granular LSTs are more likely to have advanced neoplasia, including invasive cancer, and more likely to be technically challenging to remove by EMR because of submucosal fibrosis. **E**, A small (13 mm) non-granular LST with a smooth hard appearance and some central depression (black + mark). The *arrows* point to an edge that is scarred from a previous partial resection. The lesion was removed by en bloc EMR and demonstrated high-grade dysplasia on pathology. **F**, A large non-granular LST in the ascending colon. The lesion demonstrated high-grade dysplasia and a tiny focus of invasive adenocarcinoma.

logical because these polyps contain regions that endoscopically and histologically correspond to the serrated class and the conventional adenoma class, respectively. The dysplastic area in an SSA/P is the portion with histologic features of a conventional adenoma and which endoscopically has NICE type 2 features, whereas the remainder of the polyp is NICE type 1[30] (Fig. 4). Any dysplasia (low grade or high grade) in an SSA/P constitutes a more-advanced lesion than an SSA/P without cytologic dysplasia,[27] and one that could progress rapidly to cancer.[31] The area of dysplasia often demonstrates microsatellite instability in microdissection studies.[32]

Endoscopic criteria for differentiation of HP from SSA/P have been proposed and validated in the Workgroup serrAted PolypS and Polyposis (WASP) classification[33] (Table 4 and Fig. 5), but their accuracy in differentiating HP from SSA/P in diminutive size lesions is not established. Given the substantial interobserver variation in distinguishing SSA/P from HP pathologically, and because the prevalence of SSA/P increases with lesion size, any proximal colon serrated class lesion ≥1 cm in size and interpreted pathologically as hyperplastic can be reasonably treated for surveillance purposes as an SSA/P.[34] This approach is particularly appropriate if the lesion has endoscopic features of SSA/P.[33]

TABLE 5. Implications of granular versus non-granular lateral-spreading tumors

Granular – homogeneous type	Low risk of cancer (~1%)
	Low risk of submucosal fibrosis
Granular – mixed nodular type	Intermediate risk of cancer (~ 5%)
	Higher risk of submucosal fibrosis in the nodular portion
Non-granular	Higher risk of cancer (~15%); especially if depressed
	Higher risk of submucosal fibrosis

Diminutive NICE type 1 lesions in the rectosigmoid are almost all hyperplastic,[35] which is the rationale for leaving them in place.[24] For the therapeutic colonoscopist, the key feature of SSA/Ps is their endoscopically indistinct edges, which often leads to incomplete resection using traditional polypectomy techniques (snaring without submucosal injection). This problem is easily overcome by submucosal injection of a contrast agent and use of a

TABLE 6. Pre-cancerous colorectal lesions: histology and typical shape, distribution, and relative prevalence

Lesion	Paris shape	Distribution	Prevalence	Pathology
Traditional adenomatous polyp	1p	Greater to left	Low	Mostly low-grade dysplasia
	1s	Throughout	Common	Mostly low-grade dysplasia
Flat adenomas (lesions)	2a	Greater to right	Common	Mostly low-grade dysplasia
Sessile serrated adenoma (polyp)	1s or 2a	Greater to right	Common	Pre-cancerous but distinction from hyperplastic polyps may not be reliable
Traditional serrated adenomas	1s or 1p	Greater to left	Rare	Pre-cancerous
Depressed (adenoma)	2c, 2a + 2c, 2c + 2a	Greater to right	Rare	↑↑ high-grade dysplasia and invasive carcinoma

high-definition colonoscope, which in combination allow easy tracking of the perimeter during resection.[36,37] The size threshold for performing submucosal injection in SSA/Ps should be 10 to 15 mm.[38] Piecemeal cold snare excision of non-dysplastic SSA/Ps, which is facilitated by submucosal injection, is an evolving area of interest. Cold resection largely prevents the risks of EMR. ESD is unnecessary for serrated lesions, because they almost universally lack invasive disease unless endoscopic features of dysplasia, large nodules, or depressed areas are present.

The vocabulary of polyp morphology

The morphology of colon polyps is of great importance to colonoscopists, and to a lesser degree to pathologists. The Paris classification provides a useful framework for discussing polyp shape and emphasizes the subtle nature of flat lesions (Fig. 6). Training in the Paris classification should be included in all endoscopic training as an enhancement to detection. Interobserver agreement in assigning lesions to Paris classification categories is moderately good at best,[39] but still the classification provides a useful clinical framework for discussing morphology.

Paris type 1 lesions are polyps. Paris type 2 lesions include flat (types 2a and 2b) and depressed (2c and its variants) lesions. High-detecting colonoscopists find such large numbers of diminutive flat adenomas that 2a and 1s lesions are present in approximately equal numbers.[40] Paris 2c depressed lesions are both rare and enormously important because of their very high prevalence of high-grade dysplasia and cancer relative to all other morphologies.[41] The prevalence of cancer in both Paris type 1 and 2a lesions is extremely low, whereas the prevalence of high-grade dysplasia and cancer in 2c lesions can reach 50%.[38] Depression is characterized by a sharp drop off from the elevated to depressed portions, and the total area of the depression is substantial. Much more common is the "2a pseudodepression," which has sloping edges and usually occupies a much smaller surface area, and does not extend down to or below the level of the normal mucosa adjacent to the lesion. Unlike true depressions, pseudodepressions have no importance as a predictor of advanced histology.

If a depressed lesion presents features suggestive of advanced cancer, such as ulceration or an amorphous vascular pattern, a biopsy specimen should be taken followed by surgery. On the other hand, if the surface pattern is preserved, en bloc resection should be considered in order to provide adequate staging and treatment for a possible superficial submucosal cancer.

Flat lesions extending ≥1 cm in diameter are designated in the Paris classification as LSTs, and they may have a sessile component (mixed LST). They are sometimes now called lateral-spreading lesions as the term "tumor" can be misinterpreted to mean invasive disease, and in years past they were called "carpet polyps." LSTs are further characterized as granular, with a lumpy, bumpy surface (Fig. 7) or "non-granular," with a smooth surface. Chromoendoscopy enhances the surface features and can clarify granular versus non-granular morphology. The significance of granular and non-granular is demonstrated in Table 5. Homogeneous granular lesions (like the surface of a bowl of rice crispies) have an extremely low prevalence of invasive disease at <1%. These lesions grow laterally, sometimes for very long periods of time, and a risk of invasive disease is acquired when a nodule develops (granular LST mixed nodular type). Nodules in granular LSTs are associated with an approximately 5% risk of invasive cancer[18] (Table 5). Non-granular lesions can be difficult to resect by EMR because they have a high prevalence of submucosal fibrosis and often a low mucosal profile that may defy snare capture. The prevalence of cancer is higher in non-granular LSTs, particularly those with depression. Again, a non-granular LST with depression that lacks NICE type 3 features is the best clinical indication for ESD over EMR.

The terms granular and non-granular LST are used for LSTs of the conventional adenoma class. This classification has no proven benefit in describing large SSA/Ps, which have different surface features from adenomas. Large SSA/Ps are flat or sessile in shape, almost never have significant fibrosis in the submucosa, and rarely contain cancer

in the absence of overt morphologic features of a dominant nodule, depression, or ulceration.[42]

Putting it all together

Table 6 summarizes clinically relevant information regarding pre-cancerous colorectal polyps. An effective colonoscopic withdrawal technique has 3 basic components, including continuous effort to examine the proximal sides of haustral folds, achieving adequate distention, and cleaning the mucosal surfaces.[43] However, the mechanical aspects of the withdrawal technique must be combined with complete understanding of the spectrum of pre-cancerous colorectal lesions. This understanding guides the approach and eyes of the colonoscopist. Thus, a full understanding of the Paris classification ensures awareness of the large pool of subtle lesions.

Table 6 shows that the distribution of the Paris type 2 lesions, whether conventional or serrated, is skewed toward the proximal colon. The skewed distribution of flat and depressed lesions toward the proximal colon may partly account for why colonoscopy fails to protect against proximal colon cancer as well as distal cancers.[44,45] Detailed understanding of the disease spectrum and meticulous technique lead to high adenoma detection rates. In the resection phase, understanding the implications of lesion morphology is essential to correct decision making. For example, SSA/Ps are less effectively removed by standard snaring techniques because of their indiscrete edges. At a relatively low size threshold, EMR with a contrast agent permits effective SSA/P resection. Further, SSA/Ps almost never have significant submucosal fibrosis, making EMR straightforward. If an LST is recognized endoscopically as a conventional adenoma, it is further classified as granular versus non-granular. Granular lesions have little or no submucosal fibrosis, and again, EMR will be relatively easy. Non-granular tumors have an increased risk of both cancer and submucosal fibrosis, and the knowledgeable colonoscopist anticipates the need for specific methods to counter submucosal fibrosis, (eg, avulsion[46]). Non-granular lesions demonstrating true depression have a higher risk for cancer, and ESD may be warranted if available. For both granular and non-granular tumors, the surface of the lesion should be carefully evaluated for NICE type 3 features, which should lead to endoscopic biopsy and then surgery.

Understanding clinically relevant histology guides post-resection management. Knowing that "intramucosal adenocarcinoma" and "carcinoma in situ" are not actually cancer, the colonoscopist should recommend to the pathologist that the term high-grade dysplasia be substituted. High-grade dysplasia is a benign lesion and does not warrant overreaction. Thus, a completely resected lesion with high-grade dysplasia has been cured. The informed colonoscopist takes pathologic readings of "villous" and "high-grade dysplasia" with a grain of salt, particularly in lesions <10 mm, based on high interobserver variation between pathologists.

Colonoscopists prefer the term "sessile serrated polyp," but understand that SSP and SSA are synonymous terms. Colonoscopists want SSA/Ps to be designated by pathologists as without or with cytologic dysplasia. SSA/Ps with cytologic dysplasia are often recognized as such endoscopically because of their mixed NICE type 1/NICE type 2 features. The SSA/P with cytologic dysplasia is recognized as a more advanced lesion that must be completely resected endoscopically.

To conclude, accurate and thorough understanding of the vocabulary of polyp histology and morphology classification are fundamental to the modern colonoscopist's approach to detection, resection, and post-resection management.

REFERENCES

1. Sabatino SS, White MC, Thompson TT, et al. Cancer screening test use – United States, 2013. MMWR Morb Mortal Wkly Rep 2015;64:464-8.
2. Luigiano C, Iabichino G, Pagano N, et al. For "difficult" benign colorectal lesions referred to surgical resection a second opinion by an experienced endoscopist is mandatory: a single centre experience. World J Gastrointest Endosc 2015;7:881-8.
3. LeRoy F, Manfredi S, Hamonic S, et al. Frequency of and risk factors for the surgical resection of nonmalignant colorectal polyps: a population based study. Endoscopy 2016;48:263-70.
4. Jayanna M, Burgess NG, Singh R, et al. Cost analysis of endoscopic mucosal resection vs surgery for large laterally spreading colorectal lesions. Clin Gastroenterol Hepatol 2016;14:271-8.
5. Law R, Das A, Gergory D, et al. Endoscopic resection is cost-effective compared with laparoscopic resection in the management of complex colon polyps: an economic analysis. Gastrointest Endosc 2016;83:1248-57.
6. Ahlenstiel G, Hourigan LF, Brown G, et al. Actual endoscopic versus predicted surgical mortality for treatment of advanced mucosal neoplasia of the colon. Gastrointest Endosc 2014;80:668-76.
7. Saito Y, Uraoka T, Yamaguchi Y, et al. A multi-center retrospective study of 1,111 colorectal endoscopic submucosal dissections (ESD) [abstract]. Gastrointest Endosc 2009;69:AB114.
8. Lee E, Lee JB, Lee SH, et al. Endoscopic submucosal dissection for colorectal tumors – 1000 colorectal ESD cases: one specialized institute's experiences. Surg Endosc 2013;27:31-9.
9. Oka S, Tanaka S, Saito Y, et al. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol 2015;110:697-707.
10. Spychalski M, Dziki A. Safe and efficient colorectal endoscopic submucosal dissection in European settings: is successful implementation of the procedure possible? Dig Endosc 2015;27:368-73.
11. Probst A, Golger D, Anthuber M, et al. Endoscopic submucosal dissection in large sessile lesions of the rectosigmoid: learning curve in a European center. Endoscopy 2012;44:660-7.
12. Rahmi G, Hotayt B, Chaussade S, et al. Endoscopic submucosal dissection for superficial rectal tumors: prospective evaluation in France. Endoscopy 2014;46:670-6.
13. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015;47:829-54.
14. Williams JG, Pullan RD, Hill J, et al. Management of the malignant colorectal polyp: ACPGBI position statement. Colorectal Dis 2013;15(Suppl 2):1-38.

15. Hayashi N, Tanaka S, Hewett DG, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointest Endosc 2013;78:625-32.
16. Hewett DG, Kaltenbach T, Sano Y, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology 2012;143:599-607.
17. Sano Y, Tanaka S, Kudo SE, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. Dig Endosc 2016;28:526-33.
18. Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology 2011;140:1909-18.
19. Kudo Se, Lambert R, Allen JI, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc 2008;68(Suppl):S3-47.
20. Rex DK, Alikhan M, Cummings O. Accuracy of pathologic interpretation of colorectal polyps by general pathologists in community practice. Gastrointest Endosc 1999;50:468-74.
21. Lasisi F, Mouchli A, Riddell R, et al. Agreement in interpreting villous elements and dysplasia in adenomas less than one centimetre in size. Dig Liver Dis 2013;45:1049-55.
22. Ponugoti PL, Cummings OW, Rex DK. Risk of cancer in small and diminutive colorectal polyps. Dig Liver Dis 2017;49:34-7.
23. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). British Society of Gastroenterology; Association of Coloproctology for Great Britain and Ireland. Gut 2010;59:666-89.
24. Rex DK, Kahi C, O'Brien M, et al. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointest Endosc 2011;73:419-22.
25. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology 2013;144:74-80.
26. Snover D, Ahnen DJ, Burt RW, et al. Serrated polyps of the colon and rectum and serrated ("hyperplastic") polyposis. In: Bozman FT, Carneiro F, Hruban RH, et al, eds. WHO Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System, 4th ed. Berlin: Springer-Verlag; 2010.
27. Rex D, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315-29.
28. Yao T, Sugai T, Iwashita A, et al. Histopathological characteristics and diagnostic criteria of SSA/P, project research 'potential of cancerization of colorectal serrated lesions' of Japanese Society for Cancer of the Colon and Rectum [Japanese]. Stomach and Intestine (Tokyo) 2011;46:442-8.
29. Khalid O, Radaideh S, Cumming OW, et al. Reinterpretation of histology of proximal colon polyps called hyperplastic in 2001. World J Gastroenterol 2009;15:3767-70.
30. Nanda KS, Tutticci N, Burgess N, et al. Caught in the act: endoscopic characterization of sessile serrated adenomas with dysplasia. Gastrointest Endosc 2014;79:864-70.
31. Bettington M, Walker N, Rosty C, et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. Gut 2017;66:97-106.
32. Sheridan TB, Fenton H, Lewin MR, et al. Sessile serrated adenomas with low- and high-grade dysplasia and early carcinomas: an immunohistochemical study of serrated lesions "caught in the act." Am J Clin Pathol 2006;126:564-71.
33. IJspeert JE, Bastiaansen BA, van Leerdam ME, et al. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. Dutch Workgroup serrAted polypS & Polyposis (WASP). Gut 2016;65:963-70.
34. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. United States Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844-57.
35. Ponugoti O, Lin J, Odze R, et al. Prevalence of sessile serrated adenoma/polyp in hyperplastic appearing diminutive rectosigmoid polyps. Gastrointest Endosc 2017;85:622-7.
36. Rex KD, Vemulapalli KC, Rex DK. Recurrence rates after EMR of large sessile serrated polyps. Gastrointest Endosc 2015;82:538-41.
37. Pellise M, Burgess NG, Tutticci N, et al. Endoscopic mucosal resection for large serrated lesions in comparison with adenomas: a prospective multicentre study of 2000 lesions. Gut 2016;66:644-53.
38. Rao AK, Soetikno R, Raju GS, et al. Large sessile serrated polyps can be safely and effectively removed by endoscopic mucosal resection. Clin Gastroenterol Hepatol 2016;14:568-74.
39. Van Doom SC, Hazewinkel Y, East JE, et al. Polyp morphology: an interobserver evaluation for the Paris classification among international experts. Am J Gastroenterol 2015;110:180-7.
40. Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. Gastroenterology 2007;133:42-7.
41. Rex DK. Preventing colorectal cancer and cancer mortality with colonoscopy: what we know and what we don't know. Endoscopy 2010;42:320-3.
42. Burgess NG, Pellise M, Nanda KS, et al. Clinical and endoscopic predictors of cytological dysplasia or cancer in a prospective multicentre study of large sessile serrated adenomas/polyps. Gut 2016;65:437-46.
43. Rex DK. Colonoscopic withdrawal technique is associated with adenoma miss rates. Gastrointest Endosc 2000;51:33-6.
44. Baxter NN, Warren JL, Barrett MJ, et al. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. J Clin Oncol 2012;30:2664-9.
45. Nishihara R, Ogino S, Chan AT. Colorectal-cancer incidence and mortality after screening. N Engl J Med 2013;369:2355.
46. Bassan MS, Cirocco M, Kandel G, et al. A second chance at EMR: the avulsion technique to complete resection within areas of submucosal fibrosis. Gastrointest Endosc 2015;81:757.

Received February 10, 2017. Accepted March 29, 2017.

Current affiliations: Division of Gastroenterology/Hepatology, Indiana University School of Medicine, Indianapolis, Indiana, USA (1), Digestive Endoscopy Unit, Catholic University, Rome, Italy (2), Department of Gastroenterology and Hepatology, Westmead Hospital and University of Sydney, Sydney, New South Wales, Australia (3).

Reprint requests: Douglas K. Rex, MD, Indiana University Hospital 4100, 550 North University Boulevard, Indianapolis, IN 46202.