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

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Abstract

Prevention of colorectal cancer by colonoscopy requires effective and safe insertion technique, high level detection of precancerous 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.

Introduction

About 60% of the eligible U.S. population report having undergone colonoscopy in the last 10 years (1). Many gastroenterologists spend more time performing colonoscopy than on 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, one is often surprised about the responses to fundamental questions about colorectal neoplasia. 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 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. It also stresses the implications of this vocabulary on management and follow-up, including how the endoscopic assessment of histology and morphology direct the selection of specific therapies such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and surgical resection.

1. **What are EMR and ESD?**

   Endoscopic mucosal resection (EMR) refers to submucosal fluid injection followed by en bloc or piecemeal snare resection. EMR is easier to perform than ESD (endoscopic submucosal dissection), requires less training, has a much lower risk of perforation, and a lower need for hospitalization post 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 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 compared with EMR (4-6).

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 comprises submucosal injection, but ESD does not use snare resection. Rather, 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.

2. 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 cytological 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

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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. Current U.S. National Comprehensive Cancer Center Network (NCCN) guidelines specifically state, "A malignant polyp is defined as one with cancer invading through the muscularis propria and into the submucosa (pT1). PTis is not consider 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 2). Western colonoscopists may be also 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.

3. **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 three histological 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 microns, the submucosal

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cancer is classified as "superficial." If the depth of invasion is >1000 microns, the cancer demonstrates "deep submucosal invasion." There are elements of subjectivity with this measurement as 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 greater than 10 to 20 mm. Pinning the lesion to allow proper orientation for histologic sectioning is important (12,13). When after an en bloc resection, a superficial submucosal cancer does not present lympho-vascular invasion or poor differentiation, endoscopic treatment may be considered as adequate, due to a very low risk of lymph-node metastasis. Contrarily, 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 invasion is identified after piecemeal snare resection of a flat or sessile lesion, surgical resection is often still considered because of the risk of under-staging 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, as the risk of lymph node metastasis is very low (though not zero). 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 zero. 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 microns) submucosal invasion in flat and sessile lesions are described in the Type 3 category of the NICE classification (15,16) (Table 1). Identification of NICE Type 3 features in a flat or sessile lesion is generally an indication for surgical resection (Figure 1). If surgery is planned the NICE 3 area can be biopsied to confirm invasive cancer. In Japan reliance on NICE alone to endoscopically predict cancer 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 Tean (JNET) classification for magnifying colonoscopy (17). Widespread use of the JNET classification in the west, where magnifying 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 higher risk of submucosal invasion, namely nongranular 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 its association with invasive cancer is discussed in more detail below.

As noted above, patients that 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). Nongranular 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 candidate group 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.

4. The vocabulary of conventional adenomas

The main histologic classes of precancerous colorectal neoplasia are the conventional adenomas and the serrated class lesions (Figure 2). Pathologists are generally accurate in assigning lesions to the conventional adenomas versus the serrated class (20). Experienced colonoscopists are also effective at predicting the histologic class of specific lesions using criteria such as NICE (Table 1).

Pathologists subclassify conventional adenomas according to the dysplasia grade (low versus high is the proper designation; mild-moderate-severe is out dated), 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 dysplasia grade interpretations 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 villousity 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 villousity is such that the British Society of Gastroenterology ignores these elements in their postpolypectomy surveillance guideline (23).

Although diagnoses of dysplasia grade and villousity 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). The non-granular LSTs and the depressed class of lesions are almost entirely adenomas. Adenomas are much more likely to have submucosal fibrosis compared with serrated lesions, and submucosal fibrosis is the bane of EMR. Serrated lesions present their own set of obstacles to endoscopic resection (24), but they are usually easily overcome.

5. **The vocabulary of serrated lesions**

The "serrated class" includes 3 distinct groups of lesions: hyperplastic polyps, sessile serrated polyps (also called sessile serrated adenomas), and traditional serrated adenomas (TSA) (26) (Figure 2). 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 will focus here on the hyperplastic polyps and sessile serrated polyp/adenoma, 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 TSA). Unlike the conventional adenomas and TSAs, all of the hyperplastic polyps and the overwhelming majority of sessile serrated polyps (SSP) are non-dysplastic (27). Sessile serrated polyp (SSP) is synonymous with sessile serrated adenoma (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, in fact, the great majority 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 vs 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).

The histologic differentiation of a hyperplastic polyp (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 hyperplastic polyps. Further, different histologic criteria for SSA/P are in use. For example, the World Health Organization (WHO) recommends that three abnormal crypts constitute a diagnosis of SSA/P (26), whereas an NIH consensus panel recommended that one unequivocally abnormal crypt is diagnostic of SSA/P (27), and the Japanese Pathology Society recommends that ≥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 cytological dysplasia (Table 3), a small percentage contain a region that looks like a conventional adenoma (Figure 3). In decades past, this lesion was designated a "mixed hyperplastic-adenomatous polyp," which was perfectly 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) (Figure 4). Any dysplasia (low-grade or high-grade) in an SSA/P constitutes a more advanced lesion than an SSA/P without cytological dysplasia (27), and one which 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 WASP classification (33)(Table 4, Figure 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

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treated for surveillance purposes as an SSA/P (34). This approach is particularly appropriate if the lesion had endoscopic features of SSA/P (33).

Diminutive NICE Type 1 lesions in the rectosigmoid are almost entirely 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 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/P, 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.

6. 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 (Figure 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 I lesions are polyps. Paris type II lesions include flat (types IIa and IIb) and depressed (IIc and its variants) lesions. High detecting colonoscopists find such large numbers of diminutive flat adenomas that IIa and Is lesions are present in approximately equal numbers (40).   The Paris IIc depressed lesions

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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 I and IIa lesions is extremely low, whereas the prevalence of high-grade dysplasia and cancer in IIc 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 "IIa 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 amorphous vascular pattern, these lesions should undergo biopsy and then 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 lateral spreading tumors (LSTs), and they may have a sessile component (mixed LST). They are sometimes now called lateral spreading lesions as term "tumor" can be misinterpreted to mean invasive disease, and in years past were called "carpet polyps." LSTs are further characterized as granular, which have a lumpy, bumpy surface (Figure 7) or "non-granular," which have 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).

7. Putting it all together

Table 6 summarizes clinically relevant information regarding the pre-cancerous colorectal polyps. 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 (42). However, the mechanical aspects of withdrawal technique must be combined with complete understanding of the spectrum of precancerous 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 disease spectrum and meticulous technique

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lead to high ADRs. In the resection phase, understanding the implications of lesion morphology is essential to correct decisions. 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 nongranular. Granular lesions have little or no submucosal fibrosis, and again, EMR will be relatively easy. Nongranular 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)). Nongranular lesions demonstrating true depression have a higher risk for cancer, and ESD may be warranted if available. For both granular and nongranular tumors, the surface of the lesion should be carefully evaluated for NICE type III 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 will 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 cytological dysplasia. SSA/Ps with cytological dysplasia are often recognized as such endoscopically

because of their mixed NICE 1/NICE 2 features. The SSA/P with cytological 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.

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Table 1. The NICE classification

*International NBI Classification (NICE)

	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	Thick brown vessels surrounding white structures**	Has area(s) with markedly distorted or missing vessels
Surface Pattern	Dark spots surrounded by white	Oval, tubular or branched white structures** surrounded by brown vessels	Distortion or absence of pattern
Most likely pathology	Hyperplastic or sessile polyp (adenoma)	Adenoma**	Deep submucosal invasive cancer

Table 2. 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

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 (Figure 1) 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

Table 4. The 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

Table 5. Implications of granular versus nongranular 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

Nongranular
*higher risk of cancer (~15%); especially if depressed
*higher risk of submucosal fibrosis

Table 6. The precancerous colorectal lesions: histology and typical shape, distribution, and relative prevalence

Lesion	Paris Shape	Distribution	Prevalence	Pathology
Traditional adenomatous polyp	1p 1s	Left Throughout	Low Common	Mostly LGD Mostly LGD
Flat adenomas (lesions)	2a	Greater to right	Common	Mostly LGD
Sessile serrated adenoma (polyp)	1s or 2a	Right side of colon	Common	Precancerous but distinction from HP may not be reliable
TSA	1s or 1p	Left side of colon	Rare	Precancerous
Depressed (adenoma)	2c 2a + 2c 2c + 2a	Greater to right	Rare	↑↑HGD and invasive CA

Figure legends

Figure 1. Lesions with NICE Type 3 features indicating deep submucosal invasion. In 1a most of the lesion shows Type 3 with a disrupted amorphous blood vessel pattern. The yellow line overlies an area of NICE Type 2 features indicating residual intact adenoma. In 1b 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 3 and indicative of deep submucosal invasion.

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

Figure 3. A sessile serrated polyp (SSP) with cytological dysplasia. The dysplastic portion of the polyp is the to the upper left. To the right is typical non-dysplastic SSP.

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

Figure 5. 5a and 5b are typical hyperplastic polyps. 5a and 5b pale from a paucity of blood vessels. The pits are uniform size and either pale (5a) or dark (5b). The few vessels are thin and lacy. 5c and 5d are sessile serrated polyps. The yellow line in 5c outlines an area of large open pits. The red line outlines an area with the cloud-like appearance. The arrow points to an indiscete margin and the entire surface has the irregular surface contour of a sessile serrated polyp. In 5d the arrows outline the indiscrete edges of the lesion.

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

Figure 7. 7a and 7b are granular lateral spreading tumors (LSTs). The bumpy surface of thte lesions lead to the "granular" name. Granular LSTs have a low risk of invasive cancer and are less likely to demonstrate significant submucosal fibrosis. 7a is a right colon lesion about to undergo submucal injection and 7b is a large rectal lesion. 7c is a granular LST with a large nodule. 7d is a large transverse colon non-granular LST during the process of resection. Note the smooth hard appearance of the residual lesion that leads to the "non-granular" terminology. Non-granular LSTs are more likley to have advanced neoplasia including invasive cancer and more likley to be technically challenging to remove by endoscopic mucosal resection (EMR) because of submucosal fibrosis. 7e shows 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

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and demonstrated high-grade dysplasia on pathology. Figure 7f shows a large nongranular ascending colon LST. The lesion deomonstrated high-grade dysplasia and a tiny focus of invasive adenocarcinoma.

Michael B. Wallace, MD, MPH

Editor-in-Chief

John R. Saltzman

Associate Editor

on behalf of the GIE Editorial Team

Dear Drs Wallace and Saltzman,

Ref.:   GIE-D-17-00186: The colonoscopist's guide to vocabulary of colorectal neoplasia: histology, morphology, and management

We appreciate the reviews of the above named manuscript submitted to GIE. We have revised the manuscript in response to the editors' comments and the reviews and are now resubmitting the paper to GIE. Below is our point by point response.

Editor's comment:

We thank these authors for a very thorough review. As you can see below, we received diverging peer reviews but overall favor publication after revision based on a majority of reviews. I would add to comments:

Please add "eligible" to "About 60% of the ELIGIBLE US population report having undergone colonoscopy in the last 10 years. Also please consider adding a comment from US NCCN guidelines on management of malignant polyps. This will add some additional "weight" to the article and provide some additional guideline backed recommendations.

Thanks for these suggestions. These have been made, and the NCCN guideline reference was made in accordance with your comment below.

Change "endoscopist" to "colonoscopist" for consistency.

"Thus, an expert colonoscopist is able to differentiate between a serrated and adenomatous polyp..."

This change was made throughout.

Under the section 2. The colonoscopist's vocabulary of colorectal cancer, consider

However, these terms are often misinterpreted by patients, referring physicians, and sometimes by endoscopists as cancer because they include the word "carcinoma." Current US National Comprehensive Cancer Center Network (NCCN) guidelines specifically state, "A malignant polyp is defined as one with cancer invading through the muscularis propria and into the submucosa (pT1). PTis is not consider a "malignant polyp." [https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf]."

Thanks for this excellent suggestion – we added this language.

Reviewer #1:

This review aims to describe the vocabulary utilized to categorize the endoscopic and histologic classes of colorectal lesions. In addition, the clinical implications of these descriptions is provided. The authors also attempt to clear the "confusion" created by the use of some terminology. Indeed the currently used terminology creates some confusion and leads to misconceptions, which in turn can lead to misguided clinical decisions. Unfortunately, this manuscript creates more confusion rather than clarity. Rather than reviewing the literature and describing the currently accepted terminology according to published consensus statements and guidelines, the authors provide heavy dose of expert opinion. A substantial part of the manuscript criticizes the current status (in most cases appropriately so) and then provides an opinion on how to improve things. In many cases the suggestions are very reasonable yet some lack practicality. Advising endoscopist to call their

pathologist to change the wording of the path report from the currently accepted nomenclature to what the authors believe is a better one is probably not the most productive way to deal with the problem. A consensus statement supported but GI and pathology experts endorsed on a society level seems to be a better way to alter the status quo rather that fighting the battle one pathologist at a time.

We changed the specific language of this point about telling the pathologist what terminology to use to soften it.   We agree the GI and pathology experts at the society level should meet about this. However since the feasibility and likelihood of success of such an effort are uncertain to us we decided to keep the general suggestion in place that pathology terms should serve the best interests of patients, which they will do by providing clarity.   We feel strongly that including the term "carcinoma" in the pathology description of a benign lesion does not facilitate patient care, and we kept the general tone of these statements.

Although I agree with most of the authors suggestions, some appear even more confusing than the current terminology. For example, instead of Sessile serrated adenoma (SSA) the term Sessile serrated polyp (SSP) is suggested. This does create confusion because many SSA by histology are actually non-polyoid by morphology. Therefore if for example we are dealing with one of the flat morphologies by Paris but the histology is serrated according to the proposed terminology we will have sessile serrated polyp that is non-polypoid???

This is an interesting comment and we added some language to make the reviewer's point. However, we are not "suggesting" the term "SSP". The WHO has already acknowledged the term "SSP" and states that is synonymous with "SSA". We simply stated that we prefer SSP over SSA because the great majority of these lesions are non-dysplastic and most GI docs in our experience do not understand that, perhaps because they call them SSAs and adenoma is ingrained in our GI brains as a uniformly dysplastic lesion. The reviewer notes that "SSP" can create confusion because the lesions are often flat, and clearly we agree this could create confusion.   Further, both "SSP" and "SSA" contain the word "sessile", which is also now generally used to describe "polyps" rather than flat lesions. So both SSP and SSA could by themselves create shape misunderstanding because of the word "sessile." We stand by our preference for SSP but have modified this section considerably to acknowledge the reviewer's point that we may be inserting too much of our own opinion. In particular we have converted to the use of SSA/P throughout and emphasized that the terms are each accepted, and must be understood as synonymous.

Some important definitions are not provided (what is standard polypectomy?) and some seem incomplete (injecting fluid in the sumbmucosa is not mandatory component of EMR). The topic of when to utilize EMR or ESD is discussed throughout the text but at the end there is no clarity. That is not surprising because the topic as correctly pointed by the authors is controversial but the discussion appears heavily angled towards the authors point of view. For example, the most current Japanese guidelines discussing the indications for colorectal ESD are not even mentioned or referenced.

Rather than standard polypectomy techniques we refer to "standard snaring". We did define EMR as submucosal injection followed by en bloc or piecemeal snaring, which we think is accurate in the colon. Perhaps submucosal injection is not a necessary part of esophageal EMR, but in the colon EMR is generally understood to include injection unless performed underwater. We modified this language slightly to reflect underwater EMR.

This manuscript will bring a lot of value to initiate a discussion, which hopefully will lead to the creation of a "vocabulary" that is accepted by all parties involved. In its current form is mostly an opinion piece rather than a review. Most of the statements made are not supported by provided references.

We tried to be reasonable with referencing. Admittedly the potential to add references is substantial. The editors' suggestion to add the NCCN website is helpful in this regard. It appears that all the key concepts are referenced.

Reviewer #2:

This is a review for practicing gastroenterologists that attempts to provide a lexicon for colonoscopy. Although limited to colonoscopy, the review covers many topics which are important. I agree that the review is needed. This review has some great images and helpful figures/tables. I have some specific comments for each section:

1) I think that distinction between ESD and EMR is important but I wonder if the level of detail is too much. The purpose of the review is to provide data to practicing gastroenterologists who are likely not performing ESD. So perhaps a simple explanation of ESD might suffice.

We shortened this section considerably.

2) I have similar thoughts about the section differentiating superficial and deep submucosal cancer. Is there too much emphasis on resection of these lesions?

We think this section is very important because it gets at developing a rationale for ESD. It would detract considerably from creating a state of the art understanding for the reader if we dropped it.

3) With regards to the serrated pathology section, I think that the flow diagram showing the conventional and serrated polyps is great. I would also include in the text a sentence that states

that serrated polyps should refer to the group of polyps that includes SSA/Ps, HPs and TSAs and that by itself "serrated" does not refer to SSA/Ps. This is a misconception that I see even among fellows. If I say to the fellows for example that the polyp looks serrated, meaning HP or SSA/P, and they interpret it as SSA/P.

This is a very good point and we have added material to emphasize this.

4) The section on polyp morphology is helpful. I would mention the JRSC classification and I would also mention that most adenomas we see are IIa (Rex, Helbig Gastro 2007) to put morphology in perspective.

Because the JRSC classification is older than Paris and seldom used, we are reluctant to add it. We want to keep the paper as practical and simple as possible, so we prefer to simply use Paris since it is most commonly used in clinical practice and in current polyp studies. We did add a sentence and the Rex-Helbig reference to indicate the very high prevalence of flat diminutive lesions in the colon.

Reviewer #3:

This manuscript proposes to address areas of confusion in classification of colorectal neoplasia. The images provide very helpful illustration of the polyp types. However, in its current version it is primarily an "expert opinion" piece rather than a comprehensive review, and provides some recommendations which are still considered controversial in our field, without addressing the nuances of why there remains uncertainty. Examples of these include:

1. Assessment of high grade dysplasia and low grade dysplasia for adenomas: many prominent pathologists do not believe these are reproducible and have recommended against the routine use of these terms.

We certainly made the point that there is poor interobserver agreement in interpreting dysplasia grade by pathologists. To suggest that they have passed out of use so that are comments are irrelevant seems incorrect to us. In our experience we still commonly see the terms in use in clinical practice. We see them regularly used in clinical studies of colon polyps. Our guidelines utilize dysplasia grade to determine colonoscopy surveillance intervals. So we have left this discussion in place.

2. Statement that there is high accuracy among pathologists and expert endoscopists in diagnosing sessile serrated adenomas: this is a misleading statement. The authors cite their own work but fail to cite other publications that have found correlation is poor even among expert pathologists.

We never said that. We said that pathologists are fairly accurate in placing polyps within the conventional adenoma vs serrated class (which includes both hyperplastic polyps and sessile serrated polyps/adenomas. In fact we devoted quite a bit of language to saying that there was poor agreement for classifying lesions within the serrated class (specifically HP vs SSA/P). We're quite confident that our original language was accurate in these regards.

3. Resect and discard: the authors argue that resect and discard of small adenomas is a preferred strategy but do not acknowledge concerns about generalizability and lack of data on long-term outcomes.

Actually, we did not argue that resect and discard is preferred. We consider the topic beyond the scope of this paper. This paper is about endoscopic and histologic correlates and relating terminology to clinical concepts. In this regard it seems appropriate to at least mention that the NICE classification and prediction of diminutive polyp pathology forms the basis of the resect and discard paradigm. Thus, we only mentioned the resect and discard paradigm.

4. Implication that endoscopic resection (EMR or ESD) is the preferred strategy vs surgical resection: While less invasive resections may be reasonable for some patients, the potential limitations of endoscopic resection (eg understaging) and the paucity of long term data on recurrence/survival should be specifically discussed to qualify this recommendation.

We cited a couple of the recent studies that have found that endoscopic resection is associated with lower costs and lower morbidity/mortality than surgical resection. Work from Dr Bourke's group has shown that only 30 patients with large lesions need endoscopic resection to prevent one death from surgery. We believe that the concept of endoscopic resection being preferable to surgery for benign lesions is firmly established.

5. "Many SSAs are non-dysplastic" and "Serrated lesions almost universally lack invasive disease" are misleading statements and should be qualified/rephrased.

Certainly the statement "Many SSAs are non-dysplastic" is not misleading. This is well substantiated in many studies. Only a small percentage of SSAs have cytological dysplasia. As for invasive disease we stated that it is rare to find it in SSAs in the absence of an ulcer or nodule or depression. We stand by that statement and the statement that almost all of them are removable by EMR.

The manuscript could be strengthened by reformatting into a discussion contrasting new developments in the fields of colorectal pathology and endoscopy with the limitations/unanswered questions pertinent to each new paradigm/technique.

Respectfully, this would serve a somewhat different purpose than what we would like to address in this paper.
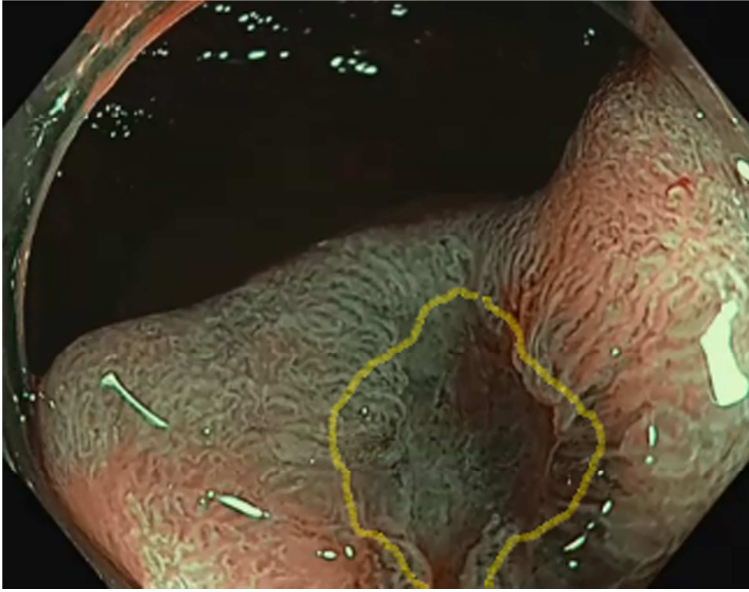
We appreciate the comments of the editors and reviewers which have enhanced the manuscript substantially, and we hope that the manuscript will now be found suitable for publication in GIE.
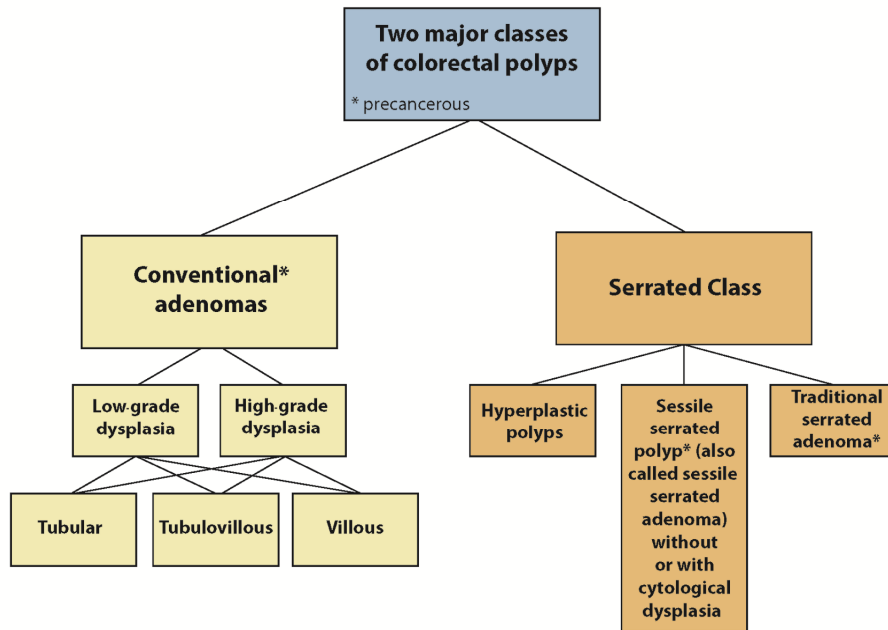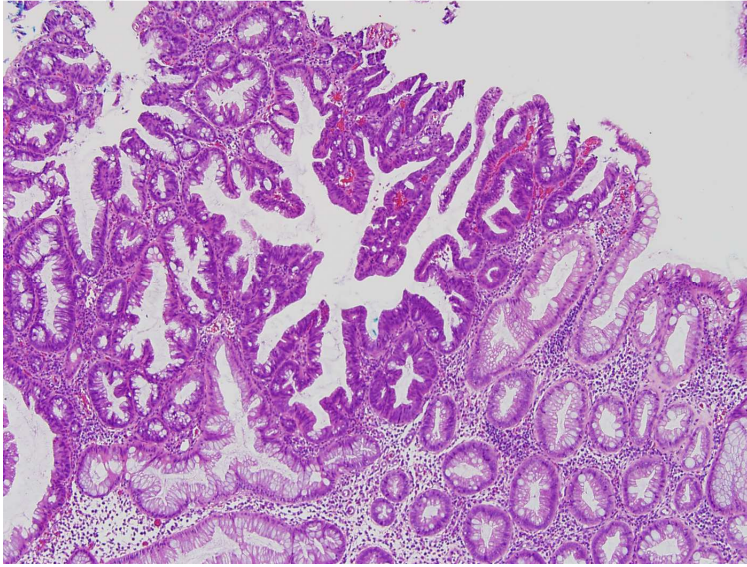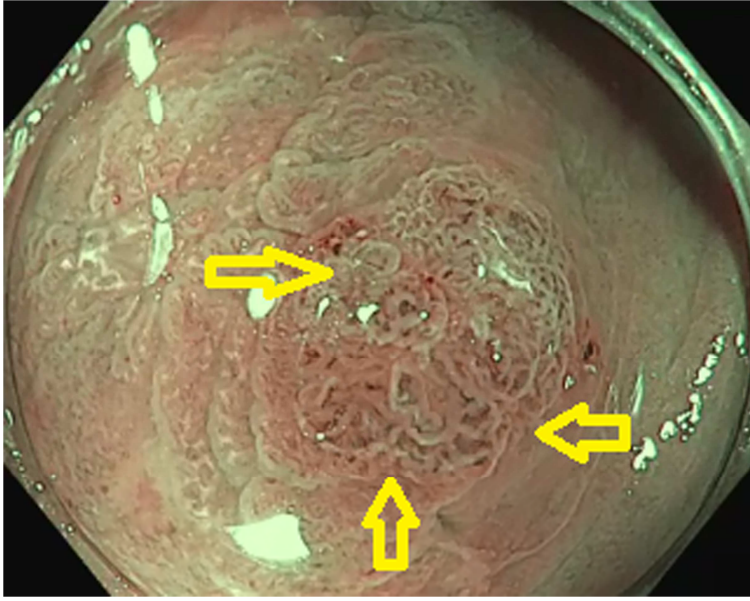
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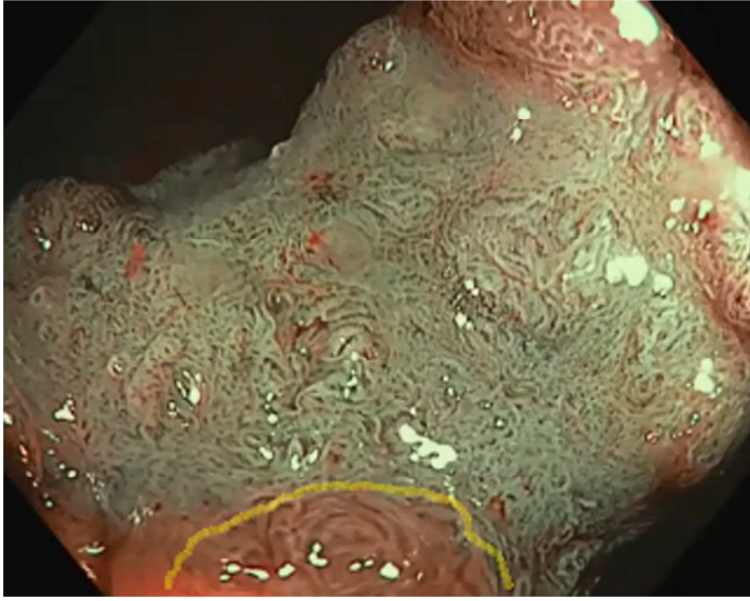
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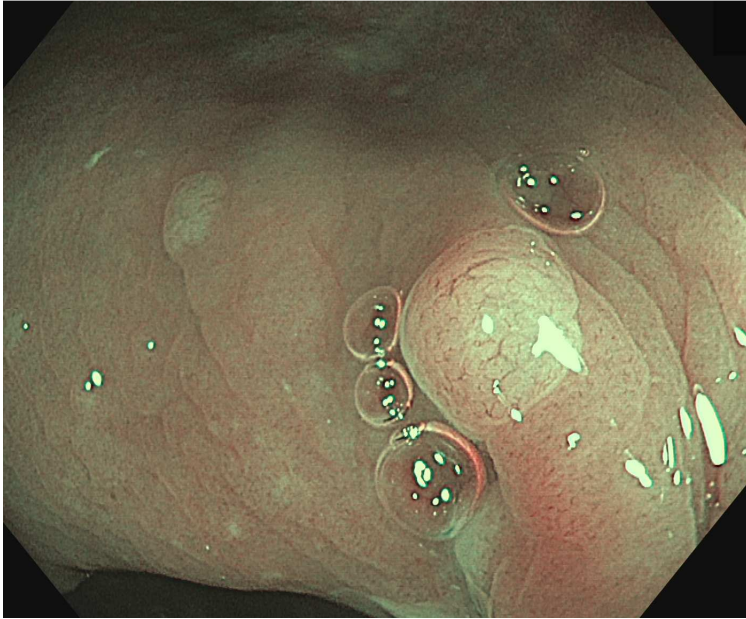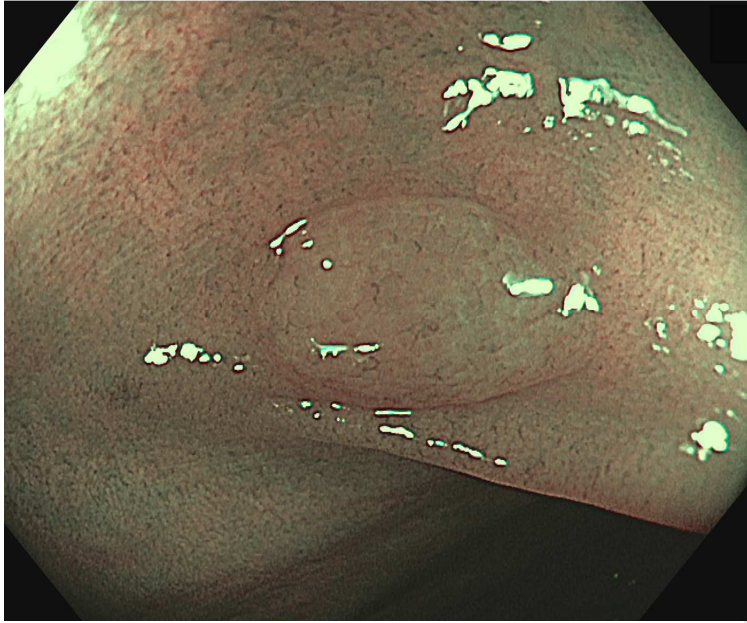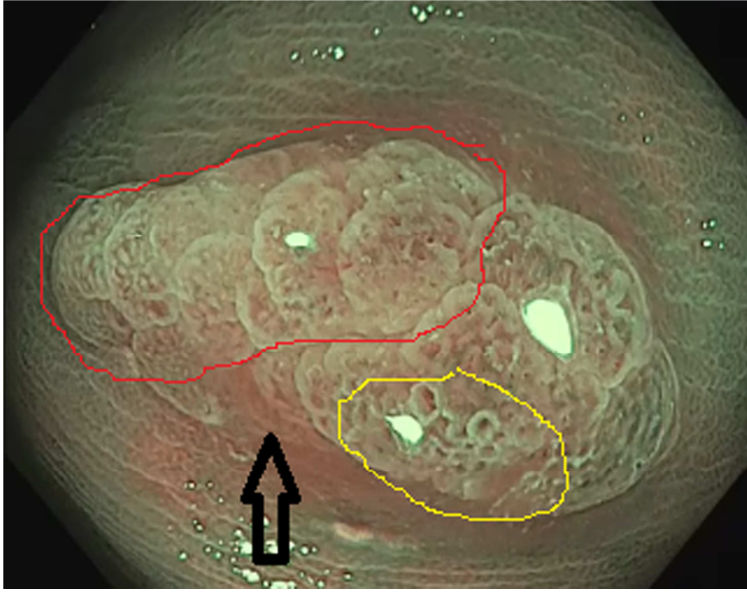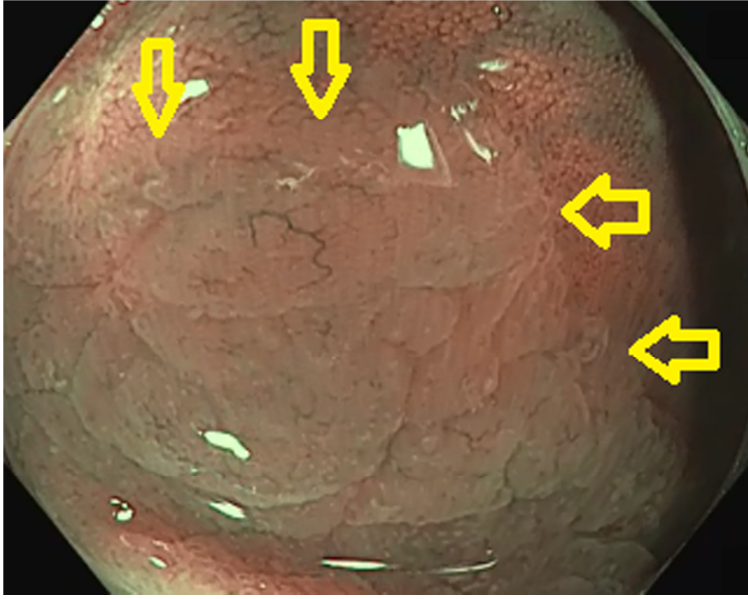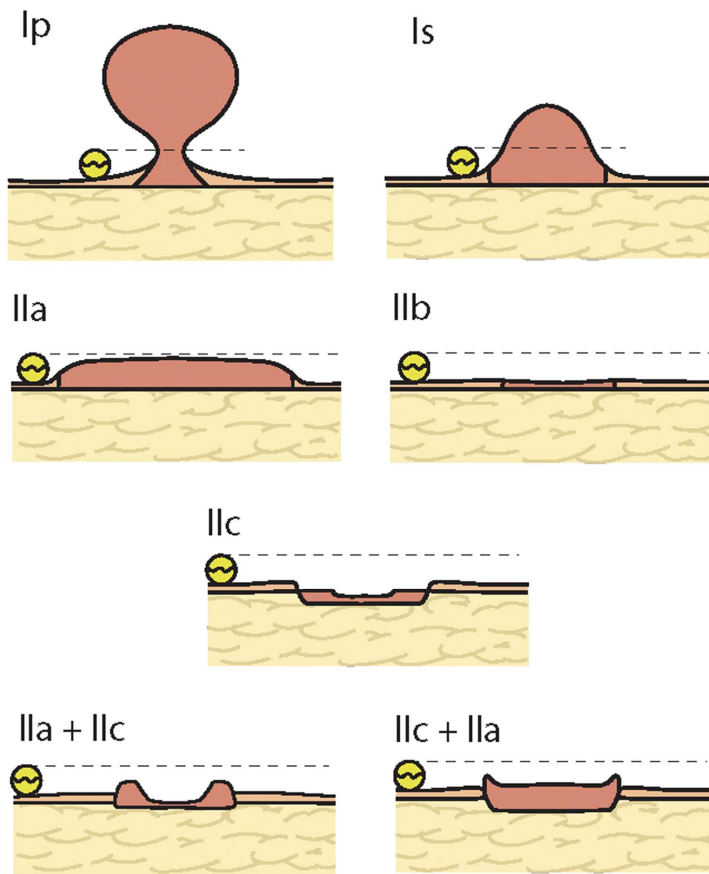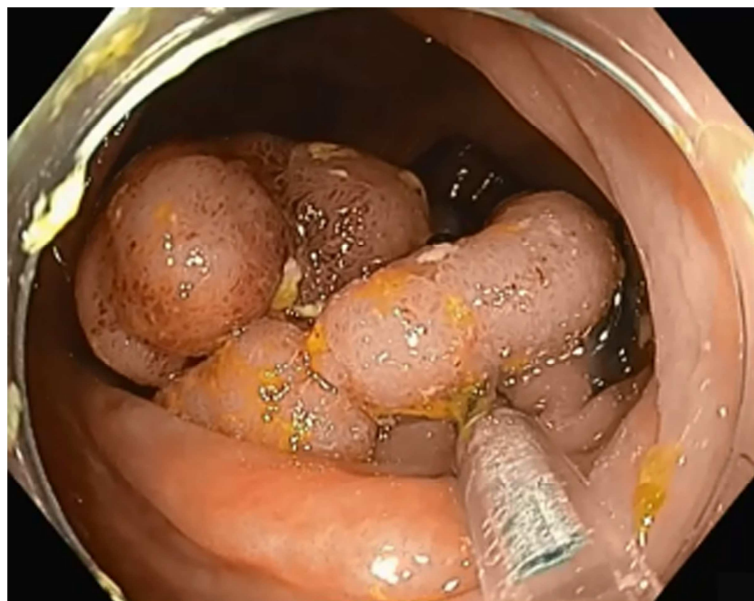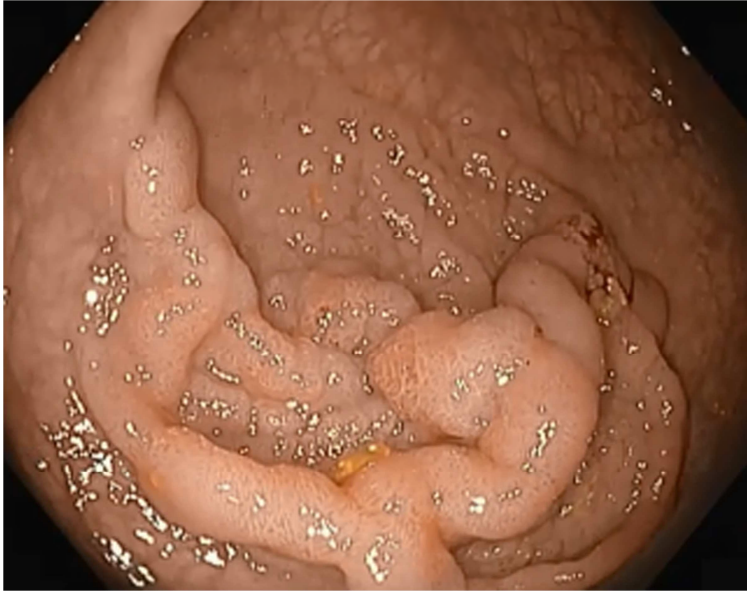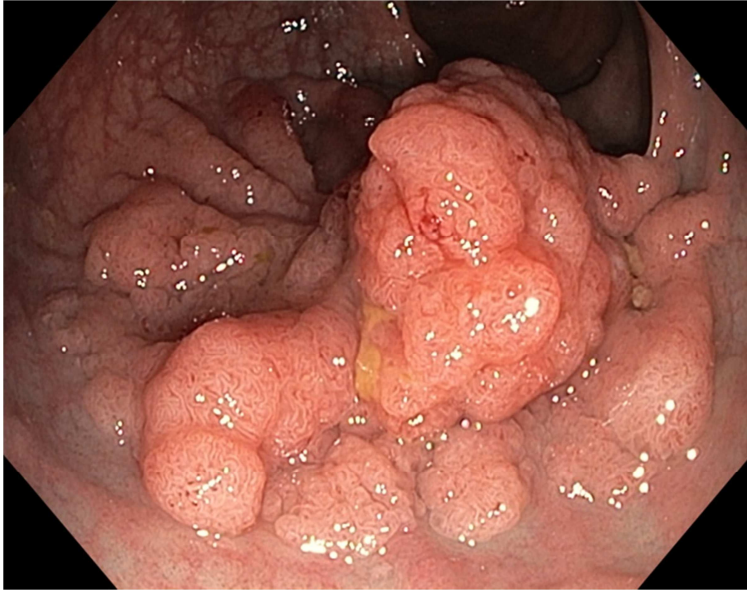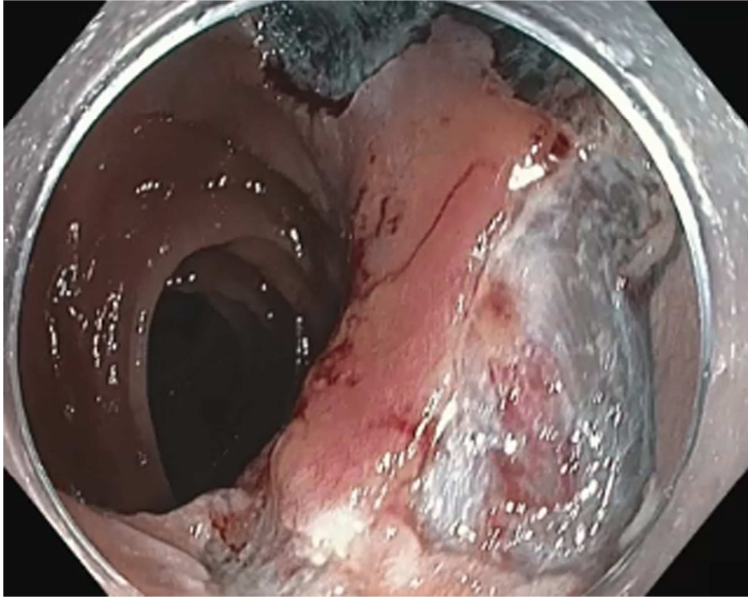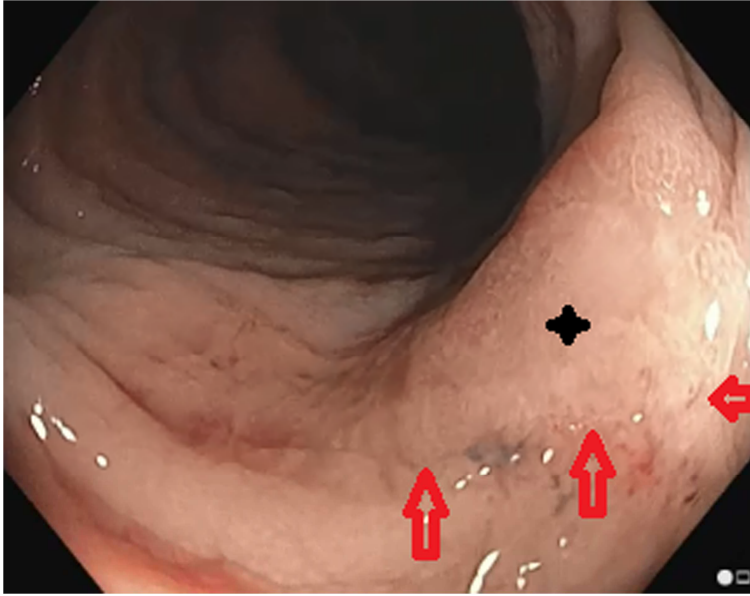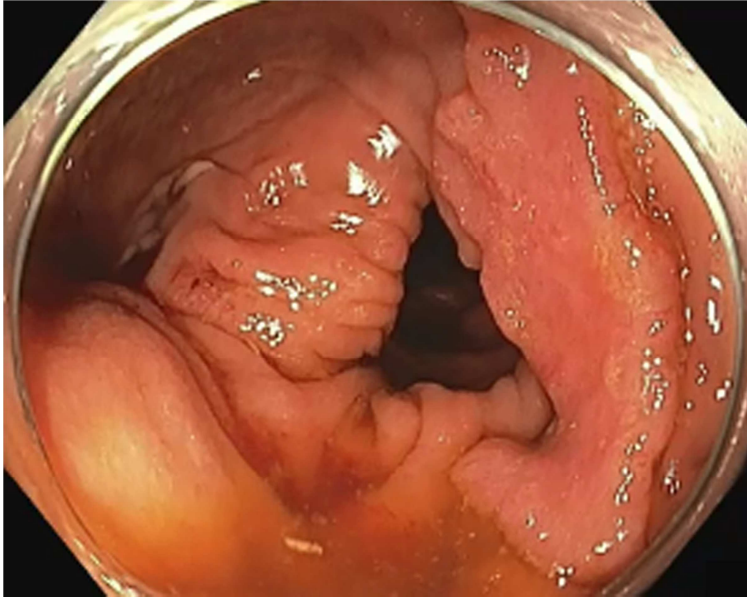
Acronyms	
CRC	Colorectal cancer
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal Dissection
CPT	Current Procedural Terminology
MM	Muscularis mucosa
JNET	Japan NBI Expert Team
NBI	Narrow band imaging
LST	Lateral spreading tumor
NICE	NBI International Colorectal Endoscopic Classification
SSP	Sessile serrated polyp
HP	Hyperplastic polyp
WHO	World Health Organization
NIH	National Institutes of Health
WASP	Workgroup serrAted polypS and Polyposis
ADR	Adenoma Detection Rate