



# Colon polyp characterization (morphology and mucosal patterns): clinical application and techniques

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**Abstract:** The endoscopic treatment of neoplastic colorectal lesions has evolved over time to include technically challenging methods such as endoscopic submucosal dissection (ESD), which is slowly gaining traction in the U.S. after relatively widespread implementation in Japan. This review broadly covers the utility and main characteristics of several modalities for the endoscopic diagnosis and treatment of colorectal polyps including white light imaging (WLI), chromoendoscopy, and narrow band imaging (NBI). The increasing utilization of these techniques has unearthed a need for comprehensive and accurate classification systems of assessment, such as Kudo's pit pattern, the Paris classification, NBI International Colorectal Endoscopic (NICE) classification, and the more recent Japan NBI Experts Team (JNET) classification. The inception and current impact of magnifying endoscopy is also considered, as it has transformed the endoscopist's ability to inspect microspheres and critically evaluate mucosal microstructures to attain an endoscopic prediagnosis. Though there are many clear advantages to existing methods of optical diagnosis, this space has not been devoid of potential problems, and the benefits as well as shortcomings are described herein. The current literature surrounding some promising applications of artificial intelligence (AI) in the detection and management of polyps, as well as in the screening of colorectal cancer (CRC), is also discussed.

**Keywords:** Colon polyp; mucosal patterns; endoscopy; classification systems

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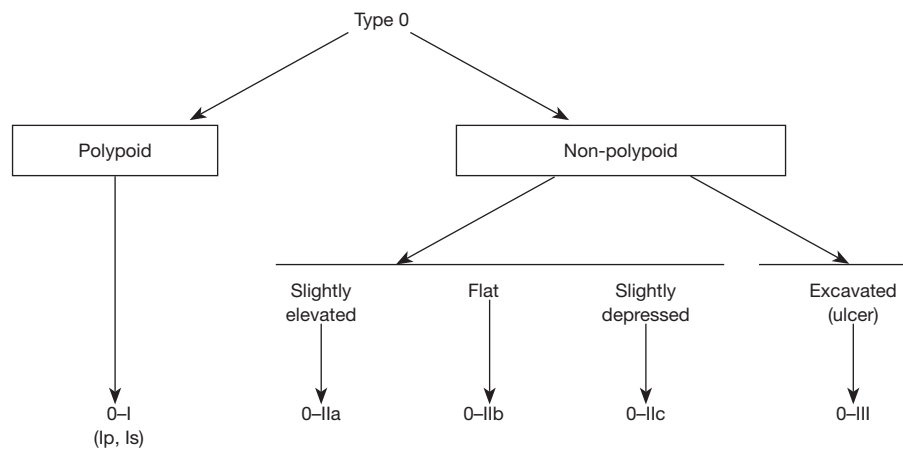
## Introduction

### Background

Colonoscopy enables not only the detection but also the endoscopic resection of colon polyps. Historically, most of the gastroenterologist's job involved detecting and

removing such polyps, fulfilling the gold standard for colorectal cancer (CRC) screening (1). However, recent advances allow the endoscopic pre-diagnosis of multiple lesion types (i.e., hyperplastic, adenomatous, serrated adenoma, and early CRC), as well as the ability to offer curative *en bloc* endoscopic resection (2). Relatively large

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**Figure 1** Paris classification of neoplastic lesions. Lesions are identified as polypoid and non-polypoid and then further described as pedunculated (0–Ip), sessile (0–Is), slightly elevated (0–IIa), flat (0–IIb), slightly depressed (0–IIc), or excavated (0–III). Reprinted from reference (9), with permission.

yet shallow lesions can be treated successfully with methods such as endoscopic submucosal dissection (ESD), if not with endoscopic mucosal resection (EMR), oftentimes averting the potential for surgery and preserving important histologic information.

### ***Rationale and knowledge gap***

Recently, what could be performed with colonoscopy has dramatically broadened. Many reports have demonstrated different ideas about its usage and importance in the accuracy of what is diagnosed and treated. In this article, we provide an overview of and discuss the current endoscopic strategies to diagnose and treat colon polyps by various modalities.

### ***Objective***

The purpose of this review is to tackle the diagnostic tools and treatment of colon polyps from a variety of perspectives.

### **Tools and treatments**

#### ***White light imaging (WLI)***

Conventional endoscopic evaluation of the colon performed with WLI allows for characterization of polyps by location, size, and morphology. Proximal colon lesions have been associated with increased risk during resection, especially in the cecum, where the risk of post-procedure complications

is highest (3). The European Society of Gastrointestinal Endoscopy recommends referral to expert centers for removal of lesions in a diverticulum, the appendix, or the ileocecal valve (4). Prior studies indicate that polyp size directly relates to cancer risk, with larger polyps harboring a higher risk of malignancy (5). Larger polyps may not be amenable to *en bloc* resection. Size of the lesion therefore may guide endoscopic resection techniques during colonoscopy, though assessment of lesion size during endoscopy is subject to high interobserver variability (6). At present, many endoscopists estimate lesion size by comparison with an open snare of a known diameter or biopsy forceps with a known length during endoscopic resection (7).

#### **Paris classification**

WLI also allows for the description of lesions by morphology. In 1998, a classification to describe the superficial endoscopic appearance of gastric lesions was devised, which was quickly applied to other lesions of the gastrointestinal (GI) tract including the colon (8). A multidisciplinary group later established a new classification scheme for polyp morphology known as the Paris classification (*Figure 1*) (9). The Paris classification broadly categorizes lesions on whether they are polypoid or non-polypoid. It further classifies polypoid lesions as pedunculated (0–Ip) or sessile (0–Is) and non-polypoid lesions as slightly elevated (0–IIa), flat (0–IIb), slightly depressed (0–IIc), or excavated (0–III) (10). Using the Paris classification during examination of lesions under WLI may predict the prognosis of lesions. The United States Multi-Society Task Force (USMSTF) suggests using

the Paris classification to furnish a common nomenclature for polyp surface morphology and recommends that every lesion larger than one cm in size is photo-documented prior to resection; the post polypectomy site should also be photo-documented (11). There is conflicting data on whether non-polypoid lesions confer a greater risk of high-grade dysplasia or early CRC (10,12-14). Other work has shown that, while rare, depressed (0-IIc) or excavated (0-III) lesions are associated with a greater risk of invasive malignancy (15). Larger, left-sided colon polyps, Paris Is-IIa, such as “...a dominant nodule within a lateral spreading tumor [LST]” have a higher risk of early invasive cancer (16). For this reason, as well as to ensure negative margins, such a lesion would necessitate the use of ESD over EMR.

### Chromoendoscopy

#### Kudo's pit pattern

Olympus Corporation's (Tokyo, Japan) release of the first magnifying colonoscope on a commercial scale transformed endoscopists' *in vivo* ability to inspect mucosal surfaces and scrutinize lesions of concern, especially those normally less apparent to the naked eye with traditional colonoscopes. Initially, 10× magnification capability was introduced (17). Reaping the benefits of the magnifying colonoscope and focusing on the relationship of pit pattern to pathological results, Kudo's pit pattern emerged as a method of making an optical diagnosis (18). This system would eventually be recognized as an accurate way to predict the pathology and estimate the depth of a lesion (19,20).

Pit patterns comprise crypt openings and microvasculature. The Kudo Classification encompasses seven distinct pit patterns: types I–V,  $V_I$ , and  $V_N$ . The first two types constitute a normal or benign appearance (non-neoplastic), whereas types III and IV are regarded as adenomatous. Finally, types  $V_I$  and  $V_N$  are considered neoplastic/cancerous (18). Accordingly, the indications for endoscopic resection include types II, III, IIII, and IV. We will point out that mild irregularity in  $V_I$  and small regionality in advanced  $V_I$  may also qualify for resection (21).

In order to better identify the pit pattern, dyes such as crystal violet (CV) may be sprayed intraluminally or applied directly to stain the mucosa (22,23). Interestingly, the original dye used by Kudo and colleagues was cresyl violet for Nissl staining, distinct from crystal or gentian violet (24,25). However, CV staining is uncommon in the U.S., given the existence of alternatives such as topical and per oral methylene blue (26), indigo carmine dye, and acetic

acid (27).

A randomized trial done in individuals at average risk of CRC demonstrated that pan-colonic chromoendoscopy with 0.4% indigo carmine spraying significantly increased the overall detection rate for adenomas, flat adenomas, and serrated lesions, as compared to standard colonoscopy, while adding nominally to procedure time. However, potential pitfalls to acknowledge are the additional training needed to skillfully implement the technique and the laborious nature of the application process (28).

Dye-based chromoendoscopy is recommended for inflammatory bowel disease (IBD) surveillance as it improves the visualization of mucosal abnormalities (29,30). When used with magnification endoscopy, it enables a better view of the mucosal crypt architecture and facilitates the application of the Kudo pit pattern classification to ultimately tell apart neoplastic and non-neoplastic lesions (29,31). Methylene blue has been employed in a randomized controlled trial as a tool for early detection of intraepithelial neoplasms and colitis-associated colon carcinomas in patients with ulcerative colitis for at least 8 years. With the aid of the modified pit pattern classification, the sensitivity and specificity of discrimination of non-neoplastic *vs.* neoplastic lesions were both 93% (32). In a prospective, randomized controlled trial of long-standing ulcerative colitis patients in remission, segmental spraying and inspection with 0.1% methylene blue did not differ significantly from narrow band imaging (NBI) in the detection of colitis-associated neoplasia (33). In a meta-analysis of the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic IBD, adding 11 minutes of procedure time to conduct topical dye spraying increased the yield of dysplasia or cancer detection by 7%. This finding was in relation to white light endoscopy and is consistent with an increased rate of the targeted yield of dysplastic lesions via chromoendoscopy; therefore, chromoendoscopy could, in turn, flag EMR-eligible lesions but does not negate the need to avoid missed dysplastic lesions via random biopsy (34).

In Japan, exceptionally high resolution, magnifying endoscopes are available and suitable for discerning Kudo's pit pattern. In contrast, such endoscopes for optical high magnification are generally unavailable or seldom used in the U.S. (24,35,36). However, Olympus released “Dual Focus” 190 series colonoscopes (CF-HQ190L/I) in the U.S. for conducting magnifying endoscopy with EMR and/or ESD, though these colonoscopes are incapable of 80× magnification. If a non-pedunculated lesion that is two cm or more in size is seen, the USMSTF recommends EMR

and that the endoscopist is seasoned in the art of advanced polypectomy (11). On the other hand, ESD supplies histopathologic information about early cancers, if present, within a polyp that would simply be unattainable after piecemeal resection.

With moderate quality evidence, the USMSTF suggests becoming proficient in electronic (i.e., NBI), dye-based (i.e., chromoendoscopy), or “...*image-enhanced endoscopy techniques to apply optical diagnosis classifications for colorectal lesion histology*” (11). NBI, a form of image-enhanced endoscopy diagnosis, is more popular than chromoendoscopy in the U.S. (35).

### *Image-enhanced endoscopy (virtual chromoendoscopy)*

#### **Flexible spectral imaging color enhancement (FICE)**

Fujifilm Corporation (Tokyo, Japan) developed FICE as a software that uses electronic optical filters during endoscopy to expose subtle details of the mucosa, as processed images display relatively high contrast between a neoplasm and its surrounding normal mucosa (37). As a form of virtual chromoendoscopy, FICE also can be used in the surveillance of IBD. The authors of a prospective, parallel arm, pragmatic trial of patients who underwent surveillance of ulcerative colitis set out to better define the role of FICE in correctly characterizing a neoplastic *vs.* non-neoplastic lesion; they found that white light endoscopy was less accurate than FICE with the modified Kudo classification at distinguishing visible lesions. FICE accurately identified 97% of non-neoplastic lesions and 93% of neoplastic lesions, and had a higher specificity as compared to white light endoscopy (29). However, a systematic review with network-meta-analysis found, with low certainty, that full spectrum high-definition white-light endoscopy had higher odds of detecting dysplastic lesions during IBD surveillance than FICE. Overall, this analysis of 2,638 patients concluded that chromoendoscopy, high-definition white-light endoscopy, NBI, autofluorescence, FICE, and full spectrum high-definition white-light endoscopy are possibly comparable options for dysplasia surveillance in IBD (38).

#### **i-SCAN**

Another image-enhanced endoscopy technology, i-SCAN, out of PENTAX (HOYA Corporation, Tokyo, Japan), also uses contrast enhancement (CE) to demarcate polyps, but has two additional possible modes for image enhancement: surface enhancement (SE) and tone enhancement (TE). i-SCAN can help conduct a detailed inspection of mucosal

structures at the push of a button without magnifying endoscopy, although it can be used adjunctively to determine the need for magnified observation, dye-spraying, or biopsy (39). A recent meta-analysis and systematic review included five studies on the impact of i-SCAN on adenoma detection rate and found that colonoscopies performed with i-SCAN with SE and CE led to a higher adenoma detection rate compared to high-definition colonoscopy. However, adenoma per subject, polyp detection rate, and polyps per subject did not reach statistical significance (40).

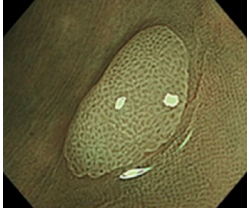
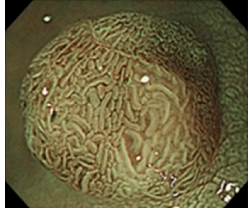
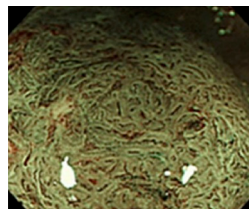
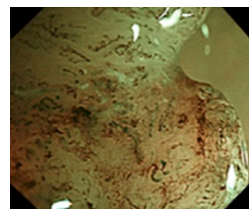
#### **NBI**

NBI was launched by Olympus in 2005 and since then has been used increasingly during endoscopy to further classify colon polyps (41). At present, the majority of Olympus endoscopes have the ability to perform NBI easily (42). Studies evaluating the use of NBI have been mixed, with some showing no significant differences in the detection of colorectal polyps compared to white-light endoscopy (43) while others have shown a significant increase in the detection of polyps with the use of NBI, especially for right-sided colon lesions (42,44).

NBI is a technique in which the wavelengths of light used for visualization are limited to a specific band. Blue and green wavelengths are specifically selected, while red light is eliminated. This technique provides improved visualization of the mucosal architecture (42,45,46). With the use of NBI, a lesion is first evaluated for a demarcation line (DL). If a DL is present, the lesion is then evaluated for irregularities in the microsurface or microvascular pattern (45). Various categorizations using NBI have been developed, including the NBI International Colorectal Endoscopic (NICE) classification and the Japan NBI Experts Team (JNET) classification, which we discuss below.

#### *NICE classification*

The NICE classification was proposed to both simplify colorectal tumor categorization and attempt to standardize it worldwide. This classification was the first NBI classification that did not mandate the use of magnifying endoscopy. Additionally, it has been used with other image-enhanced endoscopy methods in a complementary manner (47-49). It entails a unique method of diagnosis that focuses on lesion color, surface pattern, and arrangement of vessels. Color and surface pattern are not only specific but also fairly simple for endoscopists to discern (47). Vessel morphology, in particular, is of salience because angiogenesis is known

	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	• Invisible <sup>*1</sup>	• Regular caliber • Regular distribution (meshed/spiral pattern) <sup>*2</sup>	• Variable caliber • Irregular distribution	• Loose vessel areas • Interruption of thick vessels
Surface pattern	• Regular dark or white spots • Similar to surrounding normal mucosa	• Regular (tubular/branched/papillary)	• Irregular or obscure	• Amorphous areas
Most likely histology	Hyperplastic polyp/ sessile serrated polyp	Low grade intramucosal neoplasia	High grade intramucosal neoplasia/shallow submucosal invasive cancer <sup>*3</sup>	Deep submucosal invasive cancer
Endoscopic image				

**Figure 2** Table of the JNET Classification which consists of types 1, 2A, 2B, and 3. Reprinted from reference (53), with permission. Copyright 2016 by Japan Gastroenterological Endoscopy Society. <sup>\*1</sup>, if visible, the caliber in the lesion is similar to surrounding normal mucosa; <sup>\*2</sup>, micro-vessels are often distributed in a punctate pattern and well-ordered reticular or spiral vessels may not be observed in depressed lesions; <sup>\*3</sup>, deep submucosal invasive cancer may be included. JNET, Japan NBI Experts Team.

to correlate with tumor growth (50,51). These three features are grouped into type 1, 2, or 3 to aid endoscopic assessment. Each type is indicative of specific pathology. Type 1 lesions are most likely hyperplastic or sessile serrated polyps, while type 2 are probable adenomas, and type 3 likely reflect deep submucosal invasive cancer (47).

A large, multicenter prospective study examined the accuracy of the NICE classification with respect to the detection of deep lesions not amenable to endoscopic resection and greater than 10 mm in size. When paired with morphologic features, the NICE classification was found to have a specificity of at least 96% even when used by non-experts for the detection of deep lesions. Depressed, nodular mixed type, pedunculated, and ulcerated lesions, on the other hand, interfered with accuracy (52). Though useful, the NICE classification was subject to several issues raised by clinical studies, for example, redundancy of similar or identical terms for magnifying findings. Experts subsequently converged to establish the more unified JNET classification (47).

### JNET classification

To address the disadvantages of the NICE classification, the JNET classification was developed. The classification derives from its predecessor, NICE, and also shares

similarities with the Kudo pit pattern in that it hones in on both surface pattern and vessel pattern. It delineates four types which pertain to the histological features of polyps: JNET type 1, type 2A, type 2B, and type 3 (Figure 2). All types except type 3 may be considered indications for ESD. Type 1 can generally be left to follow up. Notably, the most likely histology associated with type 2B includes shallow submucosal invasive cancers and high grade intramucosal neoplasia (47). Therefore, it is thought that in comparison to the other types, type 2B is not as strong of an indicator of high-grade dysplasia and superficial submucosal carcinoma due to the heterogeneous nature of the histology it envelopes. Subtyping for type 2B has been proposed as a way to possibly improve its performance and diagnostic utility (54).

Overall, JNET undoubtedly remains a useful tool to visually evaluate tumor pathology and depth. Furthermore, its diagnostic yield and diagnostic accuracy have been thoroughly studied in the clinical setting (55-57). Additionally, the JNET classification is both reliable and validated (58,59). For these reasons, we view JNET as the final answer to questions about NBI classification.

### Other modalities for diagnosis

#### Artificial intelligence (AI)

Of late, AI has garnered attention for its real time use

in colon polyp detection and potential for decreasing the rate of CRCs. In 2020, a 14% absolute increase in adenoma detection rate was reported in a multicenter randomized controlled trial of computer-aided detection in colorectal neoplasia using Medtronic's GI Genius (60). More recently, the first ever multicenter, multi country randomized crossover trial studying adenoma miss rates (AMRs) also employed GI Genius and found that AI-assisted colonoscopy reduced AMR by almost 50% (61). Additionally, computer aided diagnosis (CADx) systems have been developed to help endoscopists implement the NICE and JNET Classifications. In these ways, AI shows promise in assisting with diagnosis of colorectal lesions (62). The body of research on AI *vs.* physicians is nascent and presently limited, but it is already apparent that AI has the potential to match or exceed performance of human doctors in colon polyp detection and diagnostic accuracy, or at least serve as a beneficial adjunct (63-66).

CADx has been applied to white-light endoscopy, magnifying NBI, magnifying chromoendoscopy, and various other technological targets to characterize polyps (67). One possible function of CADx could be to lessen the time needed by beginner endoscopists to detect neoplastic lesions (68). Even experienced proceduralists, unaided, can have trouble identifying CRCs with deep submucosal invasion (classified as T1b), which carry a risk of metastasis (69). This is because T1b lesions on plain endoscopic images may be indiscernible from those with superficial invasion or mucosal CRCs (70,71). The USMSTF suggests that proceduralists become proficient in endoscopic recognition of deep submucosal invasion (11). In one study, a CADx system was designed to tell apart T1b from Tis/T1a lesions on plain endoscopy and its performance compared to endoscopists of varying levels (ranging from trainees to experts). Overall, it performed "*slightly inferior to experts*" (69). No specific trends were identified with respect to diagnostic values determined from readings by expert endoscopists on the basis of morphology and lesion size. The CADx system demonstrated higher sensitivity for polypoid morphology than for flat morphology, but this difference was non-significant (69).

## Conclusions

Ultimately, the main goal of polypectomy is to entirely remove colorectal lesions to prevent the development of CRC, and proceduralists should select evidence based techniques that are "*...the safest, most complete, and efficient*"

to perform such resections (11). In patients with IBD, the current practice of colonoscopic surveillance entails identifying and removing precursor lesions of colorectal neoplasia to attenuate the additional CRC risk posed by this condition, though undoubtedly resource-intensive. As others have astutely pointed out, there remains a continued need to evaluate the practices of chromoendoscopy and taking random biopsies, as well as the efficacy of ESD in people diagnosed with IBD (72). As for the average risk population, once technologies such as CADx are studied with more randomized controlled trials, this will enable physicians to make confident predictions about lesions and cut down on the needless removal of minute, noncancerous polyps (73,74). It is forecasted that, in the coming years, AI will be swiftly deployed into colonoscopy practice and continue to impact the landscape of the endoscopic diagnosis and management of polyps (67).

Recent advancements in colonoscopy, imaging modalities, and AI have facilitated high-quality examination of colon lesions. Our review highlights recent updates on these modalities for detecting colorectal lesions, as well as summarizes current knowledge on their diagnostic performance. It is important to understand the features of each test and to apply them appropriately in clinical practice for optimal patient care.

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